```
=> d his

     (FILE 'HOME' ENTERED AT 09:40:56 ON 21 JAN 2008)

     FILE 'CAPLUS, MEDLINE' ENTERED AT 09:41:15 ON 21 JAN 2008
L1            70 S ADENOSINE/TI (P) ARTHRITIS/TI
L2             2 S ADENOSINE/TI (P) BONE LOSS/TI
L3            16 S ADENOSINE/TI (P) BONE RESORPTION/TI
L4             1 S PURINE DERIVATIVES/TI (P) BONE RESORPTION/TI
L5             1 S PURINE DERIVATIV?/TI (P) BONE RESORPTION/TI
L6             2 S PURINES/TI (P) BONE RESORPTION/TI
L7             0 S ADENINE DERIVATIV?/TI (P) BONE RESORPTION/TI
L8             0 S ADENINE/TI (P) BONE RESORPTION/TI
L9             3 S PURINE?/TI (P) BONE RESORPTION/TI
L10            0 S PURINE DERIVATIVE?/TI (P) BONE LOSS/TI
L11            0 S PURINE?/TI (P) BONE LOSS/TI
L12            0 S ADENINE?/TI (P) BONE LOSS/TI
L13            0 S ADENINNSINE?/TI (P) BONE LOSS/TI
L14            2 S ADENOSINE?/TI (P) BONE LOSS/TI
L15            2 S PURINE?(P) BONE RESORPTION (P) PREVENT?
L16           10 S PURINE?(P) BONE RESORPTION (P) TREAT?
L17           24 S PURINE?(P) BONE RESORPTION
L18           14 S L17 NOT L16
L19           22 S ADENINE? (P) BONE RESORPTION
L20           22 S L19 NOT L3
```

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=> d his

     (FILE 'HOME' ENTERED AT 11:27:14 ON 21 JAN 2008)

     FILE 'REGISTRY' ENTERED AT 11:27:38 ON 21 JAN 2008
L1             STRUCTURE UPLOADED
L2          50 S L1 SSS SAM
L3       91204 S L1 SSS FULL
L4             STRUCTURE UPLOADED
L5          50 S L4 SSS SAM
L6       15650 S L4 SSS FULL

     FILE 'CAPLUS, MEDLINE' ENTERED AT 11:31:20 ON 21 JAN 2008
L7      280832 S L3
L8         383 S L3 AND BONE RESORPTION
L9          26 S L8 AND PREVENT?
L10        146 S L8 AND TREAT?
L11       9516 S L6
L12         19 S L11 AND BONE RESORPTION
```

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=> d his

     (FILE 'HOME' ENTERED AT 12:10:50 ON 21 JAN 2008)

     FILE 'REGISTRY' ENTERED AT 12:11:00 ON 21 JAN 2008
L1             STRUCTURE UPLOADED
L2          50 S L1 SSS SAM
L3       14257 S L1 SSS FUL

     FILE 'CAPLUS, MEDLINE' ENTERED AT 12:11:42 ON 21 JAN 2008
L4           3 S L3 AND BONE RESORPTION
L5           0 S L3 AND BONE LOSS
L6           3 S L3 AND OSTEOARTHRITIS
L7           0 S L3 AND BONE REDUCTION
L8           0 S L3 AND LOSS OF BONE
L9           0 S L3 AND BONE DECREASE?
```
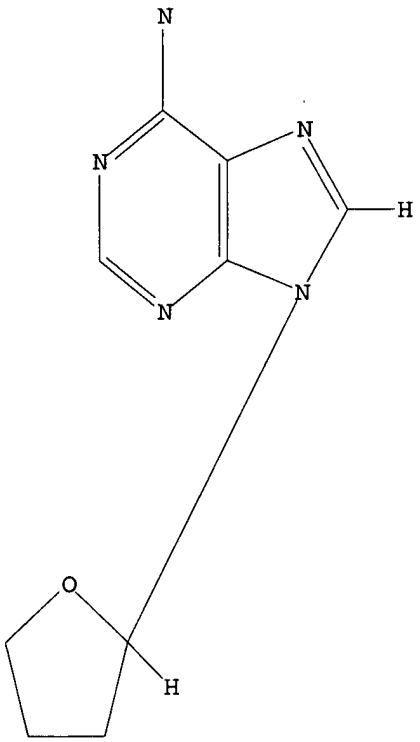
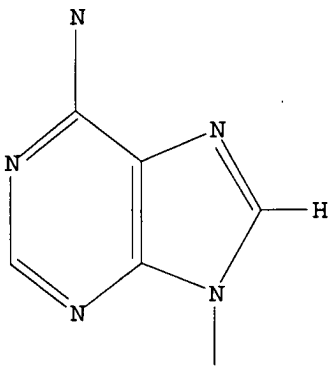

```
=> d his

     (FILE 'HOME' ENTERED AT 12:39:23 ON 21 JAN 2008)

     FILE 'REGISTRY' ENTERED AT 12:39:38 ON 21 JAN 2008
L1             STRUCTURE UPLOADED
L2          15 S L1 SSS SAM
L3         315 S L1 SSS FULL

     FILE 'CAPLUS, MEDLINE' ENTERED AT 12:40:39 ON 21 JAN 2008
L4           0 S L3 AND BONE RESORPTION?
L5           0 S L3 AND BONE LOSS
L6             STRUCTURE UPLOADED

     FILE 'REGISTRY' ENTERED AT 12:44:45 ON 21 JAN 2008
L7             STRUCTURE UPLOADED
L8          50 S L7
L9        2072 S L7 SSS FULL

     FILE 'CAPLUS, MEDLINE' ENTERED AT 12:46:07 ON 21 JAN 2008
L10      10358 S L9
L11          0 S L10 AND BONE RESPRPTION
L12          7 S L10 AND BONE RESORPTION
L13          0 S L10 AND BONE LOSS
L14         10 S L10 AND OSTEOARTHRITIS?
```

=> d l1
L1 HAS NO ANSWERS
L1 STR



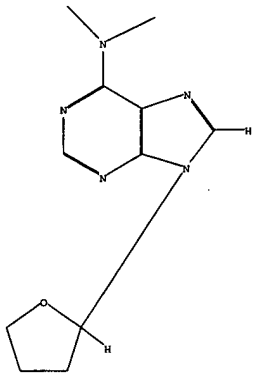
Structure attributes must be viewed using STN Express query preparation.

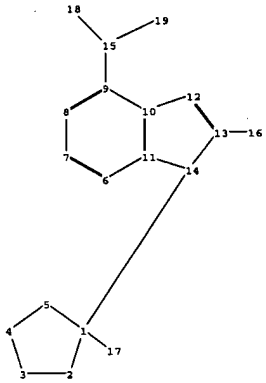
=> d L4
L4 HAS NO ANSWERS
L4 STR



Structure attributes must be viewed using STN Express query preparation.

C:\Program Files\Stnexp\Queries\10564620-e.str





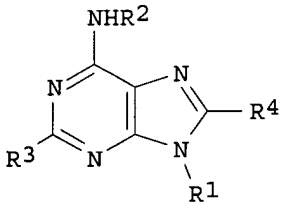
chain nodes :
15 16 17 18 19
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14
chain bonds :
1-14 1-17 9-15 13-16 15-18 15-19
ring bonds :
1-2 1-5 2-3 3-4 4-5 6-7 6-11 7-8 8-9 9-10 10-11 10-12 11-14 12-13 13-14
exact/norm bonds :
1-2 1-5 1-14 2-3 3-4 4-5 9-15 10-12 11-14 12-13 13-14 15-18 15-19
exact bonds :
1-17 13-16
normalized bonds :
6-7 6-11 7-8 8-9 9-10 10-11

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom 12:Atom 13:Atom 14:Atom 15:CLASS 16:CLASS 17:CLASS 18:CLASS 19:CLASS

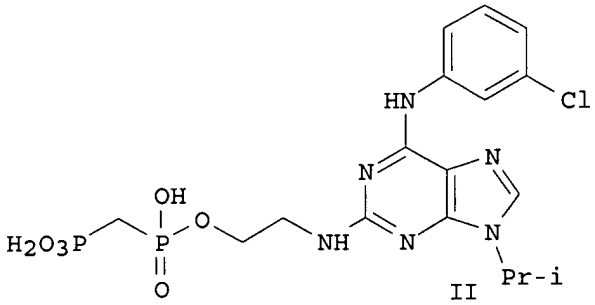
4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:429543 CAPLUS
DOCUMENT NUMBER: 137:6038
TITLE: Preparation of purine derivatives as bone resorption inhibitors
INVENTOR(S): Weigele, Manfred; Sawyer, Tomi K.; Bohacek, Regine; Shakespeare, William C.; Sundaramoorthi, Rajeswari; Wang, Yihan; Dalgarno, David C.; Metcalf, Chester A.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 99 pp., Cont.-in-part of U.S. Ser. No. 740,267.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2002068721	A1	20020606	US 2000-740393		20001218
US 7115589	B2	20061003			
US 2002103161	A1	20020801	US 2000-740267		20001218
US 2002132819	A1	20020919	US 2000-740653		20001218
AT 327242	T	20060615	AT 2000-986551		20001218
US 2005096298	A1	20050505	US 2004-994962		20041122
PRIORITY APPLN. INFO.:			US 1999-172161P	P	19991217
			US 1999-172510P	P	19991217
			US 2000-240788P	P	20001016
			US 2000-740267	A2	20001218
			US 2000-740653	A2	20001218
			US 2000-740619	A	20001218

OTHER SOURCE(S): MARPAT 137:6038
GI



I



II

AB Purine derivs. of formula I [R1 = H, aliphatic, heteroaliph., aryl, or heteroaryl moiety; R2 = aliphatic, heteroaliph., aryl, or heteroaryl moiety; R3, R4 = H, halo, (substituted) OH, (substituted) NH, (substituted) SH, aliphatic, heteroaliph., aryl, or heteroaryl moiety] are prepared for use as bone resorption inhibitors. Thus, II was prepared from 2-amino-6-chloropurine, 2-propanol, 3-chloroaniline, ethanolamine and methylenebis(phosphonic dichloride). The preferred compds. I have IC50 values below 500 nM in the anti-resorption cell assay on white rabbits.
REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=>

L1 ANSWER 65 OF 70 MEDLINE on STN
ACCESSION NUMBER: 81104583. MEDLINE
DOCUMENT NUMBER: PubMed ID: 6256964
TITLE: [Cyclic 3',5'-adenosine monophosphate in the liver of rats with experimental rheumatoid arthritis].
Tsiklicheskii 3',5'-adenozinmonofosfat v pecheni krys s eksperimental'nym revmatoidnym artritom.
AUTHOR: Iusipova N A; Goncharik L A; Balakleevskii A I; Surikov P M; Bezkrovnaia V G
SOURCE: Voprosy medit sinskoi khimii, (1980 Nov-Dec) Vol. 26, No. 6, pp. 767-70.
Journal code: 0416601. ISSN: 0042-8809.
PUB. COUNTRY: USSR
DOCUMENT TYPE: (COMPARATIVE STUDY)
(ENGLISH ABSTRACT)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Russian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198103
ENTRY DATE: Entered STN: 16 Mar 1990
Last Updated on STN: 16 Mar 1990
Entered Medline: 27 Mar 1981

AB Content of cAMP was distinctly decreased in rat liver tissue within the first days of development of experimental rheumatoid arthritis (adjuvant arthritis). Within 6 days the content of cAMP was slightly increased in liver tissue of the arthritic rats but it was lowered 2-fold as compared with controls. The content of cAMP was quite unaltered during subsequent course of the impairment (within 25 days). In blood plasma of patients with rheumatoid arthritis the content of cAMP was decreased more than 2-fold as compared with its concentration in blood of donors. Possible importance of cAMP deficiency in pathogenesis of rheumatoid arthritis is discussed.

L1 ANSWER 66 OF 70 MEDLINE on STN
ACCESSION NUMBER: 81103116 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6256850
TITLE: The effect of fasting on plasma cyclic adenosine -3', 5'-monophosphate in rheumatoid arthritis.
AUTHOR: Trang L E; Lovgren O; Bendz R; Mjos O
SOURCE: Scandinavian journal of rheumatology, (1980) Vol. 9, No. 4, pp. 229-33.
Journal code: 0321213. ISSN: 0300-9742.
PUB. COUNTRY: Sweden
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198103
ENTRY DATE: Entered STN: 16 Mar 1990
Last Updated on STN: 16 Mar 1990
Entered Medline: 24 Mar 1981

AB Cyclic adenosine-3', 5'-monophosphate (cAMP) may influence important mechanisms in the inflammatory process, and fasting has been claimed to be clinically beneficial in rheumatoid arthritis (RA). A study was therefore designed to measure the concentrations of plasma cAMP in RA patients not undergoing drug treatment during a control and a fasting period. Twelve female RA patients were hospitalized for two 14-day periods and investigated in a crossover study. Clinical and laboratory variables of inflammatory activity were assessed during both periods. During the control period the concentrations of cAMP in plasma were slightly below the lower normal limit, with no significant change throughout the period. The clinical and laboratory variables of inflammatory activity were

unchanged during the same period. In the fasting period, the prefasting level of plasma cAMP was significantly higher than on the corresponding day in the control period. During 7 days of total fasting the plasma cAMP concentrations decreased significantly. The clinical and laboratory variables of inflammatory activity decreased significantly from the start to the end of fasting. High prefasting plasma cAMP concentrations were associated with improvement in clinical inflammatory activity. A decrease in plasma cAMP concentrations during fasting in RA patients is in contrast to the findings in obese and healthy subjects previously reported.

L1 ANSWER 67 OF 70 MEDLINE on STN
ACCESSION NUMBER: 69195237 MEDLINE
DOCUMENT NUMBER: PubMed ID: 4388973
TITLE: Plasma adenosine deaminase activity in children with rheumatic fever and rheumatoid arthritis.
AUTHOR: Krawczynska H; Raczynska J; Krawczynski J
SOURCE: Polish medical journal, (1969) Vol. 8, No. 2, pp. 261-7. Journal code: 0376721. ISSN: 0032-2938.
PUB. COUNTRY: Poland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 196907
ENTRY DATE: Entered STN: 1 Jan 1990
Last Updated on STN: 6 Feb 1998
Entered Medline: 9 Jul 1969

L1 ANSWER 68 OF 70 MEDLINE on STN
ACCESSION NUMBER: 69031236 MEDLINE
DOCUMENT NUMBER: PubMed ID: 5688485
TITLE: [Activity of adenosine desaminase in the plasma of children with rheumatic fecer and rheummatoid arthritis].
Aktywnosc dezaminazy adenozyny w osoczu dzieci chorych na chorobe reumatyczna i gosciec przewlekly postepujacy.
AUTHOR: Krawczynska H; Raczynska J; Krawczynski J
SOURCE: Polski tygodnik lekarski (Warsaw, Poland : 1960), (1968 Jul 15) Vol. 23, No. 29, pp. 1089-92. Journal code: 9705468. ISSN: 0032-3756.
PUB. COUNTRY: Poland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Polish
FILE SEGMENT: Priority Journals
ENTRY MONTH: 196812
ENTRY DATE: Entered STN: 1 Jan 1990
Last Updated on STN: 1 Jan 1990
Entered Medline: 30 Dec 1968

L1 ANSWER 69 OF 70 MEDLINE on STN
ACCESSION NUMBER: 69016288 MEDLINE
DOCUMENT NUMBER: PubMed ID: 5303164
TITLE: [Activity of adenosine deaminase in the serum of children ill with rheumatism and chronic progressive arthritis].
Aktivita adenosin-desaminazy v seru u deti nemocnych revmatismem a chronickou progresivni artritidou.
AUTHOR: Krawczynska H; Raczynska J; Krawczynski J
SOURCE: Ceskoslovenska pediatrie, (1968 Sep) Vol. 23, No. 9, pp. 821-6. Journal code: 0403576. ISSN: 0069-2328.
PUB. COUNTRY: Czechoslovakia
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Czech
FILE SEGMENT: Priority Journals

ENTRY MONTH: 196812
ENTRY DATE: Entered STN: 1 Jan 1990
Last Updated on STN: 6 Feb 1998
Entered Medline: 9 Dec 1968

L1 ANSWER 70 OF 70 MEDLINE on STN
ACCESSION NUMBER: 62044686 MEDLINE
DOCUMENT NUMBER: PubMed ID: 13903318
TITLE: Adenosine triphosphatase activity in blood in rheumatoid arthritis.
AUTHOR: GYORKI J; SANDELL B M
SOURCE: Acta rheumatologica Scandinavica, (1961) Vol. 7, pp. 127-30.
Journal code: 0321403. ISSN: 0001-6934.
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: OLDMEDLINE; NONMEDLINE
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 16 Jul 1999
Last Updated on STN: 16 Jul 1999
Entered Medline: 1 Nov 1998

L1 ANSWER 55 OF 70 MEDLINE on STN
ACCESSION NUMBER: 94245451 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8188457
TITLE: Effect of cyclosporin on the activity of cytidine deaminase and adenosine deaminase in the serum and polymorphonuclear leukocytes of patients with rheumatoid arthritis.
AUTHOR: Stancikova M; Rovensky J
CORPORATE SOURCE: Research Institute of Rheumatic Diseases, Piest'any, Slovak Republic.
SOURCE: International journal of tissue reactions, (1993) Vol. 15, No. 4, pp. 169-74.
Journal code: 8302116. ISSN: 0250-0868.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199406
ENTRY DATE: Entered STN: 29 Jun 1994
Last Updated on STN: 29 Jun 1994
Entered Medline: 23 Jun 1994

AB Cytidine deaminase (CDA) and adenosine deaminase (ADA) were investigated in the serum and polymorphonuclear leukocytes (PMNLs) of healthy controls and ten patients with rheumatoid arthritis before and during cyclosporin therapy. CDA was significantly raised in the serum and decreased in the cells of patients. A dramatic increase (10-fold or more) in CDA activity was observed in the cells of some patients after only one month of cyclosporin therapy. Serum CDA significantly increased after three months' therapy. While the increase in serum CDA level during therapy was transient, the enzyme level in cells remained permanently raised, as shown in two patients evaluated for sixteen months. ADA in the serum of RA patients was somewhat higher as compared with healthy controls and remained almost unchanged during cyclosporin therapy. ADA activity in the cells also increased, but compared with the increase in CDA activity this increase was lower. Cyclosporin increased both CDA and ADA activities in PMNLs of RA patients. The dramatic increase in CDA observed in PMNLs of patients could be the cause of the transient increase in CDA in the serum. Further investigations will show to what extent this property of cyclosporin can reflect the immunoregulatory effect of this drug.

L1 ANSWER 56 OF 70 MEDLINE on STN
ACCESSION NUMBER: 92150730 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1784774
TITLE: [Adenosine deaminase activity in tuberculous arthritis and other monoarthritis].
Actividad de adenosina desaminasa en artritis tuberculosa y otras monoartritis.
AUTHOR: Telenti M; Fernandez B de Quiros J; Junquera M; Santos Rionda M J
SOURCE: Revista clinica espanola, (1991 Apr) Vol. 188, No. 7, pp. 384-5.
Journal code: 8608576. ISSN: 0014-2565.
PUB. COUNTRY: Spain
DOCUMENT TYPE: Letter
LANGUAGE: Spanish
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199203
ENTRY DATE: Entered STN: 5 Apr 1992
Last Updated on STN: 5 Apr 1992
Entered Medline: 19 Mar 1992

L1 ANSWER 57 OF 70 MEDLINE on STN
ACCESSION NUMBER: 91292039 MEDLINE

DOCUMENT NUMBER: PubMed ID: 2490482
TITLE: [Adenosine deaminase in tuberculous arthritis].
Adenosindeaminasa en la artritis tuberculosa.
AUTHOR: Oristrell J; Larrosa M; Santesmasses A; Torra M; Segura F
SOURCE: Enfermedades infecciosas y microbiologia clinica, (1989 Nov) Vol. 7, No. 9, pp. 515-6.
Journal code: 9104081. ISSN: 0213-005X.
PUB. COUNTRY: Spain
DOCUMENT TYPE: (CASE REPORTS)
Letter
LANGUAGE: Spanish
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199108
ENTRY DATE: Entered STN: 1 Sep 1991
Last Updated on STN: 3 Feb 1997
Entered Medline: 15 Aug 1991

L1 ANSWER 58 OF 70 MEDLINE on STN
ACCESSION NUMBER: 89129869 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2851868
TITLE: [Possible role of cyclic adenosine -3',5'-monophosphate in the pathogenesis of rheumatoid arthritis].
O vozmozhnoi roli tsiklicheskogo adenozin-3',5'-monofosfata v patogeneze revmatoidnogo artrita.
AUTHOR: Matveikov G P; Iusipova N A; Bezkrovnaia V G
SOURCE: Revmatologiia (Moscow, Russia), (1988 Jul-Sep) No. 3, pp. 20-4.
Journal code: 8309921. ISSN: 0233-7029.
PUB. COUNTRY: USSR
DOCUMENT TYPE: (ENGLISH ABSTRACT)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Russian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198903
ENTRY DATE: Entered STN: 8 Mar 1990
Last Updated on STN: 8 Mar 1990
Entered Medline: 23 Mar 1989

L1 ANSWER 59 OF 70 MEDLINE on STN
ACCESSION NUMBER: 88251157 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3382270
TITLE: Serum and synovial fluid adenosine deaminase activity in patients with rheumatoid arthritis, osteoarthritis, and reactive arthritis.
AUTHOR: Yuksel H; Akoglu T F
CORPORATE SOURCE: Department of Medicine, Marmara University Medical School, Istanbul, Turkey.
SOURCE: Annals of the rheumatic diseases, (1988 Jun) Vol. 47, No. 6, pp. 492-5.
Journal code: 0372355. ISSN: 0003-4967.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198807
ENTRY DATE: Entered STN: 8 Mar 1990
Last Updated on STN: 8 Mar 1990
Entered Medline: 21 Jul 1988
AB Adenosine deaminase activity was determined in paired samples of serum and synovial fluid taken from patients with rheumatoid arthritis (n = 12), reactive arthritis (n = 13), and osteoarthritis (n = 7), and the value of this investigation in the diagnosis of synovial swellings was assessed.

Increased activity was found in the synovial fluid taken from patients with rheumatoid disease and reactive arthritis, though values were less raised in the latter. Synovial fluid taken from patients with osteoarthritis did not show significantly raised adenosine deaminase activity as compared with that of normal controls (n = 3).

L1 ANSWER 60 OF 70 MEDLINE on STN
ACCESSION NUMBER: 87130969 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3815464
TITLE: [Adenosine deaminase activity in the lymphocytes of patients with gouty arthritis].
Aktivita adenozindeaminazy v lymfocytoch pacientov s arthritis urica.
AUTHOR: Mikulikova D; Pechan I; Bosmansky K; Ondrasik M; Bosak V
SOURCE: Casopis lekar u c eskych, (1986 Nov 14) Vol. 125, No. 46, pp. 1405-8.
Journal code: 0004743. ISSN: 0008-7335.
PUB. COUNTRY: Czechoslovakia
DOCUMENT TYPE: (ENGLISH ABSTRACT)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Slovak
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198704
ENTRY DATE: Entered STN: 3 Mar 1990
Last Updated on STN: 3 Mar 1990
Entered Medline: 1 Apr 1987

L1 ANSWER 61 OF 70 MEDLINE on STN
ACCESSION NUMBER: 86237576 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3487181
TITLE: [Adenosine deaminase activity in levamisole treatment of patients with rheumatoid arthritis].
Die Adenosindesaminase-Aktivitat unter Levamisol-Behandlung von Patienten mit Rheumatoid-Arthritis.
AUTHOR: Seidel W; Kruger W
SOURCE: Zeitschrift fur die gesamte innere Medizin und ihre Grenzgebiete, (1986 Mar 15) Vol. 41, No. 6, pp. 172-4.
Journal code: 21730470R. ISSN: 0044-2542.
PUB. COUNTRY: GERMANY, EAST: German Democratic Republic
DOCUMENT TYPE: (ENGLISH ABSTRACT)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198606
ENTRY DATE: Entered STN: 21 Mar 1990
Last Updated on STN: 21 Mar 1990
Entered Medline: 27 Jun 1986
AB Nine patients who fell ill with a classical or unequivocal rheumatoid arthritis were treated with 150 mg Levamisol a week. Before the beginning of the therapy and on the day after the fourth intake of medicaments the activity of the adenosine deaminase in lymphocytes, erythrocytes and in the plasma was determined. An influence on the enzyme activity by Levamisol could not be proved. Before as well as after the Levamisol therapy the enzyme activity in the erythrocytes was diminished.

L1 ANSWER 62 OF 70 MEDLINE on STN
ACCESSION NUMBER: 86035434 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3877119
TITLE: Effects of pentostatin (2'deoxycoformycin), an inhibitor of adenosine deaminase, on type II collagen-induced arthritis in rats.
AUTHOR: Gilbertsen R B
SOURCE: Journal of immunopharmacology, (1985) Vol. 7, No. 3, pp. 325-41.

Journal code: 7901853. ISSN: 0163-0571.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198512
ENTRY DATE: Entered STN: 21 Mar 1990
Last Updated on STN: 21 Mar 1990
Entered Medline: 13 Dec 1985

AB Pentostatin (2'-deoxycoformycin), a potent inhibitor of adenosine deaminase, was administered therapeutically to rats with type II collagen-induced arthritis and the effects on hindpaw swelling, serum haptoglobin concentration, and anticollagen antibody titer determined. Daily intraperitoneal administration of pentostatin at 10.0 or 1.0 mg/kg/day for three weeks produced significant enhancement of hind-paw swelling and elevation of serum haptoglobin. Continuous subcutaneous infusion of pentostatin at 1.0 or 0.1 mg/kg/day had the same effects. None of the dosing regimens had any effect on anticollagen antibody titer.

L1 ANSWER 63 OF 70 MEDLINE on STN
ACCESSION NUMBER: 84260763 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6744969
TITLE: Pleural fluid adenosine deaminase in rheumatoid arthritis and systemic lupus erythematosus.
AUTHOR: Pettersson T; Klockars M; Weber T
SOURCE: Chest, (1984 Aug) Vol. 86, No. 2, pp. 273-4.
Journal code: 0231335. ISSN: 0012-3692.
PUB. COUNTRY: United States
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198409
ENTRY DATE: Entered STN: 20 Mar 1990
Last Updated on STN: 20 Mar 1990
Entered Medline: 5 Sep 1984

L1 ANSWER 64 OF 70 MEDLINE on STN
ACCESSION NUMBER: 81225136 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6264559
TITLE: [Adenosine cyclic monophosphate (cAMP) levels in the lymphocytes of rheumatoid arthritis patients].
Zachowanie sie poziomu cyklicznego adenozynomonofosforanu (cAMP) w limfocytach chorych na reumatoidalne zapalenie stawow.
AUTHOR: Zajaczek-Grabowska A; Grabczewska E; Krzystyniak K; Ryzewski J; Maldyk H
SOURCE: Reumatologia, (1980) Vol. 18, No. 4, pp. 377-83.
Journal code: 20130190R. ISSN: 0034-6233.
PUB. COUNTRY: Poland
DOCUMENT TYPE: (ENGLISH ABSTRACT)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Polish
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198108
ENTRY DATE: Entered STN: 16 Mar 1990
Last Updated on STN: 16 Mar 1990
Entered Medline: 10 Aug 1981

L2 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:1014365 CAPLUS

DOCUMENT NUMBER: 147:462137

TITLE: Comparative analysis of the effects of a novel vacuolar adenosine 5'-triphosphatase inhibitor, FR202126, and doxycycline on bone loss caused by experimental periodontitis in rats

AUTHOR(S): Niikura, K.

CORPORATE SOURCE: Data Management and Regulatory Support Department, Astellas Research Service, Ibaraki, Japan

SOURCE: Journal of Periodontology (2006), 77(7), 1211-1216
CODEN: JOPRAJ; ISSN: 0022-3492

PUBLISHER: American Academy of Periodontology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Doxycycline is reported to inhibit alveolar bone destruction by blocking matrix metalloproteinases (MMPs). Nevertheless, MMPs are not involved in osteoclastic bone resorption; osteoclasts directly resorb bone. An acidic microenvironment, which is formed by vacuolar adenosine 5'-triphosphatase (V-ATPase) expressed in the plasma membranes of osteoclasts, is indispensable for osteoclastic bone resorption. In the present study, we investigated the potential role of the acidic environment on periodontal bone destruction using a novel and specific V-ATPase inhibitor, FR202126, which we compared to doxycycline. Inhibitory activity against in vitro bone resorption was examined by measuring the Ca2+ release from murine calvariae cultured for 6 days, which were treated with interleukin-1 (IL-1), IL-6, or parathyroid hormone. Exptl. periodontitis was induced by a ligature wire tied around the contact between the first and second maxillary molars of male Wistar rats. FR202126 and doxycycline were administered orally once daily for 6 days. Seven days after typing, the maxillae were dissected and mesiodistal longitudinal paraffin sections, including interdental alveolar bone, were processed for histopathol. anal. FR202126 inhibited bone resorption almost completely in calvaria cultures induced by three stimulators, whereas doxycycline was unable to prevent in vitro bone resorption. Oral administration of FR202126 significantly prevented alveolar bone loss in exptl. periodontitis. However, doxycycline did not inhibit alveolar bone destruction. These results suggest that an acidic microenvironment plays a more important role than MMPs in periodontal alveolar bone destruction and that V-ATPase inhibitors may offer a new approach to the treatment of periodontal disease.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:1014365 CAPLUS
DOCUMENT NUMBER: 147:462137
TITLE: Comparative analysis of the effects of a novel vacuolar adenosine 5'-triphosphatase inhibitor, FR202126, and doxycycline on bone loss caused by experimental periodontitis in rats
AUTHOR(S): Niikura, K.
CORPORATE SOURCE: Data Management and Regulatory Support Department, Astellas Research Service, Ibaraki, Japan
SOURCE: Journal of Periodontology (2006), 77(7), 1211-1216
CODEN: JOPRAJ; ISSN: 0022-3492
PUBLISHER: American Academy of Periodontology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Doxycycline is reported to inhibit alveolar bone destruction by blocking matrix metalloproteinases (MMPs). Nevertheless, MMPs are not involved in osteoclastic bone resorption; osteoclasts directly resorb bone. An acidic microenvironment, which is formed by vacuolar adenosine 5'-triphosphatase (V-ATPase) expressed in the plasma membranes of osteoclasts, is indispensable for osteoclastic bone resorption. In the present study, we investigated the potential role of the acidic environment on periodontal bone destruction using a novel and specific V-ATPase inhibitor, FR202126, which we compared to doxycycline. Inhibitory activity against in vitro bone resorption was examined by measuring the Ca2+ release from murine calvariae cultured for 6 days, which were treated with interleukin-1 (IL-1), IL-6, or parathyroid hormone. Exptl. periodontitis was induced by a ligature wire tied around the contact between the first and second maxillary molars of male Wistar rats. FR202126 and doxycycline were administered orally once daily for 6 days. Seven days after typing, the maxillae were dissected and mesiodistal longitudinal paraffin sections, including interdental alveolar bone, were processed for histopathol. anal. FR202126 inhibited bone resorption almost completely in calvaria cultures induced by three stimulators, whereas doxycycline was unable to prevent in vitro bone resorption. Oral administration of FR202126 significantly prevented alveolar bone loss in exptl. periodontitis. However, doxycycline did not inhibit alveolar bone destruction. These results suggest that an acidic microenvironment plays a more important role than MMPs in periodontal alveolar bone destruction and that V-ATPase inhibitors may offer a new approach to the treatment of periodontal disease.
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 2 OF 2 MEDLINE on STN
ACCESSION NUMBER: 2006389929 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16805684
TITLE: Comparative analysis of the effects of a novel vacuolar adenosine 5'-triphosphatase inhibitor, FR202126, and doxycycline on bone loss caused by experimental periodontitis in rats.
AUTHOR: Niikura K
CORPORATE SOURCE: Data Management and Regulatory Support Department, Astellas Research Service, Ibaraki, Japan.. kazuaki.niikura@jp.astellas.com
SOURCE: Journal of periodontology, (2006 Jul) Vol. 77, No. 7, pp. 1211-6.
Journal code: 8000345. ISSN: 0022-3492.
PUB. COUNTRY: United States
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Dental Journals; Priority Journals

ENTRY MONTH: 200609
ENTRY DATE: Entered STN: 30 Jun 2006
Last Updated on STN: 14 Sep 2006
Entered Medline: 13 Sep 2006

AB BACKGROUND: Doxycycline is reported to inhibit alveolar bone destruction by blocking matrix metalloproteinases (MMPs). Nevertheless, MMPs are not involved in osteoclastic bone resorption; osteoclasts directly resorb bone. An acidic microenvironment, which is formed by vacuolar adenosine 5'-triphosphatase (V-ATPase) expressed in the plasma membranes of osteoclasts, is indispensable for osteoclastic bone resorption. In the present study, we investigated the potential role of the acidic environment on periodontal bone destruction using a novel and specific V-ATPase inhibitor, FR202126, which we compared to doxycycline. METHODS: Inhibitory activity against in vitro bone resorption was examined by measuring the Ca2+ release from murine calvariae cultured for 6 days, which were treated with interleukin-1 (IL-1), IL-6, or parathyroid hormone. Experimental periodontitis was induced by a ligature wire tied around the contact between the first and second maxillary molars of male Wistar rats. FR202126 and doxycycline were administered orally once daily for 6 days. Seven days after tying, the maxillae were dissected and mesiodistal longitudinal paraffin sections, including interdental alveolar bone, were processed for histopathologic analysis. RESULTS: FR202126 inhibited bone resorption almost completely in calvaria cultures induced by three stimulators, whereas doxycycline was unable to prevent in vitro bone resorption. Oral administration of FR202126 significantly prevented alveolar bone loss in experimental periodontitis. However, doxycycline did not inhibit alveolar bone destruction. CONCLUSION: These results suggest that an acidic microenvironment plays a more important role than MMPs in periodontal alveolar bone destruction and that V-ATPase inhibitors may offer a new approach to the treatment of periodontal disease.

L3 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1972:367 CAPLUS
DOCUMENT NUMBER: 76:367
ORIGINAL REFERENCE NO.: 76:79a,82a
TITLE: Role of adenosine-3',5'-monophosphate in the hormonal regulation of bone resorption. Cultured fetal bone
AUTHOR(S): Klein, David C.; Raisz, Lawrence G.
CORPORATE SOURCE: Sch. Med. Dent., Univ. Rochester, Rochester, NY, USA
SOURCE: Endocrinology (1971), 89(3), 818-26
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The release of radiocalcium from fetal long bone shafts in tissue culture is stimulated by addition of parathyroid hormone (PTH, 0.01-0.1 μM). This effect can be mimicked by addition of N6-2'-O-dibutyryl adenosine-3',5'-monophosphate (dibutyryl cyclic AMP) [362-74-3] at concns. of 0.1-0.3 mM, but not by adenosine 3',5'-monophosphate (cyclic AMP) [60-92-4] itself. Dibutyryl cyclic AMP lost its effectiveness at higher concns. (0.8-1.0 mM) due to autoinhibition. Theophylline [58-55-9] alone did not stimulate bone resorption. It increased the release of labeled calcium [7440-70-2] in the presence of low doses of PTH. Dibutyryl cyclic AMP and theophylline may increase cyclic AMP levels by inhibiting phosphodiesterase; this could stimulate bone resorption at low concns. and cause autoinhibition by activation of the thyrocalcitonin-sensitive system at higher concns.

L3 ANSWER 9 OF 16 MEDLINE on STN
ACCESSION NUMBER: 2006532317 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16956430
TITLE: IB-MECA, an A3 adenosine receptor agonist prevents bone resorption in rats with adjuvant induced arthritis.
AUTHOR: Rath-Wolfson L; Bar-Yehuda S; Madi L; Ochaion A; Cohen S; Zabutti A; Fishman P
CORPORATE SOURCE: Can-Fite BioPharma Ltd., Kiryat-Matalon, Petah-Tikva, Israel.
SOURCE: Clinical and experimental rheumatology, (2006 Jul-Aug) Vol. 24, No. 4, pp. 400-6.
Journal code: 8308521. ISSN: 0392-856X.
PUB. COUNTRY: Italy
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200612
ENTRY DATE: Entered STN: 8 Sep 2006
Last Updated on STN: 19 Dec 2006
Entered Medline: 12 Dec 2006
AB OBJECTIVES: The anti-inflammatory effect of adenosine is partially mediated via the A3 adenosine receptor (A3AR), a Gi protein associated cell surface receptor. The highly selective A3AR agonist, IB-MECA was earlier shown to prevent the clinical and pathological manifestations of arthritis in experimental animal models of collagen and adjuvant induced arthritis (AIA). In this study we tested the effect of IB-MECA on the prevention of bone resorption in AIA rats and looked at the molecular mechanism of action. METHODS: Rats with AIA were treated orally twice daily with IB-MECA starting upon onset of disease and the clinical score was evaluated every other day. At study termination the foot, knee and hip region of both vehicle and IB-MECA treated animals were subjected to histomorphometric analysis. Western blot analysis was carried out on paw protein extracts. RESULTS: IB-MECA ameliorated the clinical manifestations of the disease and reduced pannus and fibrosis formation, attenuated cartilage and bone destruction and decreased the number of

osteoclasts. In cell protein extracts derived from paw of AIA rats, A3AR was highly expressed in comparison to naive animals. In paw extracts derived from IB-MECA treated AIA rats, down-regulation of the A3AR protein expression level was noted. PI3K, PKB/Akt, IKK, NF-kappaB, TNF-alpha and RANKL were down-regulated whereas caspase 3 was up-regulated. CONCLUSION: IB-MECA, a small highly bioavailable molecule, induces modulation of proteins which control survival and apoptosis resulting in the amelioration of the inflammatory process and the preservation of bone mass in AIA rats.

L3 ANSWER 10 OF 16 MEDLINE on STN
ACCESSION NUMBER: 93312334 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8391806
TITLE: The cyclic-AMP antagonist adenosine-3',5'-cyclic monophosphosphorothioate, RP-isomer inhibits parathyroid hormone induced bone resorption, in vitro.
AUTHOR: Ljunggren O; Ljunghall S
CORPORATE SOURCE: Department of Internal Medicine, University Hospital, Uppsala, Sweden.
SOURCE: Biochemical and biophysical research communications, (1993 Jun 30) Vol. 193, No. 3, pp. 821-6.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199308
ENTRY DATE: Entered STN: 13 Aug 1993
Last Updated on STN: 3 Feb 1997
Entered Medline: 5 Aug 1993
AB Stimulation of osteoclastic bone resorption is mediated via the osteoblasts. In order to investigate the second messenger events that cause the osteoblasts to initiate bone resorption we have evaluated the effect of the cyclic AMP antagonist adenosine-3'5'-cyclic monophosphosphorothioate, Rp-isomer (Rp-cAMPS) on bone resorption in vitro, by measuring the release of prelabelled 45Ca from cultured neonatal mouse calvarial bones. Forskolin (FSK, at and above 10 nM), an agent that enhances cyclic AMP-formation, stimulated bone resorption in 96 h cultures. Addition of Rp-cAMPS to the incubation media dose-dependently inhibited bone resorption induced by FSK (0.5 microM), with total inhibition obtained at 30 microM Rp-cAMPS. Bone resorption stimulated by parathyroid hormone (PTH, 0.1-10 nM, 72 h) was also inhibited by Rp-cAMPS (30 microM), while bone resorption induced by 1.25(OH)2D3 (1-10 nM, 72 h) was unaffected by Rp-cAMPS. These data demonstrate that PTH and 1,25(OH)2D3 cause bone resorption via different mechanisms and that cyclic AMP is the major second messenger in PTH-induced bone resorption.

L3 ANSWER 11 OF 16 MEDLINE on STN
ACCESSION NUMBER: 91198536 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1964815
TITLE: H(+)-stimulated release of prostaglandin E2 and cyclic adenosine 3',5'-monophosphoric acid and their relationship to bone resorption in neonatal mouse calvaria cultures.
AUTHOR: Rabadjija L; Brown E M; Swartz S L; Chen C J; Goldhaber P
CORPORATE SOURCE: Harvard School of Dental Medicine, Boston, MA 02115.
CONTRACT NUMBER: AG-02899 (NIA)
DK 36796 (NIDDK)
SOURCE: Bone and mineral, (1990 Dec) Vol. 11, No. 3, pp. 295-304.
Journal code: 8610542. ISSN: 0169-6009.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)

(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199105
ENTRY DATE: Entered STN: 7 Jun 1991
Last Updated on STN: 7 Jun 1991
Entered Medline: 22 May 1991

AB The addition of protons to the medium of neonatal mouse calvaria cultures stimulated bone resorption and release of calcium into the medium. In addition, added protons significantly increased the release of prostaglandin E2 (PGE2) and cyclic adenosine 3',5'-monophosphoric acid (cAMP) from the bones. Indomethacin significantly inhibited the release of calcium, PGE2 and cAMP from proton-treated cultures. The positive control, parathyroid hormone (PTH)-treated cultures, also gave rise to bone resorption and calcium release into the medium. However, unlike the addition of protons, the addition of PTH did not stimulate PGE2 release nor did indomethacin inhibit calcium release from PTH-treated cultures. In addition, indomethacin only slightly inhibited cAMP release from PTH-treated cultures, as compared to the marked inhibition by indomethacin of cAMP release from proton-treated cultures. These findings indicate that bone resorption due to added protons is dependent on both PGE2 and cAMP production, whereas bone resorption due to PTH only involves cAMP production.

L3 ANSWER 12 OF 16 MEDLINE on STN
ACCESSION NUMBER: 88045842 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2823534
TITLE: Characterization of adenosine receptors in bone. Studies on the effect of adenosine analogues on cyclic AMP formation and bone resorption in cultured mouse calvaria.
AUTHOR: Lerner U H; Sahlberg K; Fredholm B B
CORPORATE SOURCE: Department of Oral Pathology, University of Umea, Sweden.
SOURCE: Acta physiologica Scandinavica, (1987 Oct) Vol. 131, No. 2, pp. 287-96.
Journal code: 0370362. ISSN: 0001-6772.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198712
ENTRY DATE: Entered STN: 5 Mar 1990
Last Updated on STN: 3 Mar 2000
Entered Medline: 16 Dec 1987

AB The effect of different adenosine analogues on cyclic AMP (cAMP) formation and bone resorption in cultured mouse calvarial bones was investigated. 5'-N-ethylcarboxamidoadenosine (NECA), R-N6-phenylisopropyl-adenosine (PIA), N6-cyclohexyl-adenosine (CHA) and 2-chloroadenosine all stimulated cyclic AMP formation with a threshold close to 1 mumol l-1); NECA was the most potent agonist. Theophylline (10, 100 mumol l-1) inhibited the cAMP accumulation induced by NECA and 2-chloroadenosine (30 and 300 mumol l-1), dose dependently. There was no inhibition of cAMP formation by PIA and CHA in forskolin-treated bone tissue. SQ 22, 536 and 2',5'-dideoxyadenosine (100 mumol l-1) both inhibited rolipram-stimulated cAMP formation. Cyclic AMP accumulation in isolated osteoblast-like cells from neonatal mouse calvarial bones was stimulated by NECA (10 and 100 mumol l-1) and 2-chloroadenosine (100 mumol l-1). 2-chloroadenosine (10 and 30 mumol l-1), but not NECA, PIA nor CHA, caused a dose-dependent stimulation of 45Ca release in both 48- and 120-h culture. The effect of 2-chloroadenosine on 45Ca release could not be antagonized by theophylline. Neither NECA, PIA, CHA nor 2-chloroadenosine could affect PTH-stimulated 45Ca release in short term cultures (6, 24 h). By contrast, stimulation of cAMP formation by forskolin or dibutyryl cAMP

caused a rapid (6 h) inhibition of PTH-stimulated bone resorption. The results demonstrate functional A2 and P-site receptors in mouse calvaria and osteoblast-like cells, but no A1-receptor was detected. These adenosine receptors regulate cAMP, but are not intimately linked to bone resorption. The calcium mobilization induced by 2-chloroadenosine appears to be unrelated to adenosine receptors.

L3 ANSWER 13 OF 16 MEDLINE on STN
ACCESSION NUMBER: 83157353 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6187560
TITLE: Vasoactive intestinal peptide stimulates bone resorption via a cyclic adenosine 3',5'-monophosphate-dependent mechanism.
AUTHOR: Hohmann E L; Levine L; Tashjian A H Jr
CONTRACT NUMBER: AM-10206 (NIADDK)
CA-17309 (NCI)
SOURCE: Endocrinology, (1983 Apr) Vol. 112, No. 4, pp. 1233-9.
Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198305
ENTRY DATE: Entered STN: 18 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 5 May 1983

L3 ANSWER 14 OF 16 MEDLINE on STN
ACCESSION NUMBER: 81211886 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6263578
TITLE: Comparison of inhibition of bone resorption and escape with calcitonin and dibutyryl 3',5' cyclic adenosine monophosphate.
AUTHOR: McLeod J F; Raisz L G
CONTRACT NUMBER: AM-18063 (NIADDK)
SOURCE: Endocrine research communications, (1981) Vol. 8, No. 1, pp. 49-59.
Journal code: 0426337. ISSN: 0093-6391.
PUB. COUNTRY: United States
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198108
ENTRY DATE: Entered STN: 16 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 10 Aug 1981
AB Both parathyroid hormone (PTH) and calcitonin (CT) can increase the concentration of cyclic 3',5' adenosine monophosphate (cAMP) in fetal rat bone in organ culture. Moreover, dibutyryl cAMP (dbcAMP) can both stimulate and inhibit 45Ca release from such bones depending on dose and experimental conditions. In this study we compared dbcAMP and CT for their effects on bones pretreated with PTH. Both compounds produced transient inhibition of bone resorption followed by escape. Escape from dbcAMP was independent of prostaglandin synthesis, since it occurred both in the presence and absence of indomethacin, a prostaglandin cyclo-oxygenase inhibitor.

L3 ANSWER 15 OF 16 MEDLINE on STN
ACCESSION NUMBER: 75091750 MEDLINE
DOCUMENT NUMBER: PubMed ID: 4374992

TITLE: The effect of phenytoin on parathyroid extract and 25-hydroxycholecalciferol-induced bone resorption: adenosine 3, 5 cyclic monophosphate production.
AUTHOR: Jenkins M V; Harris M; Wills M R
SOURCE: Calcified tissue research, (1974) Vol. 16, No. 2, pp. 163-7.
Journal code: 0114414. ISSN: 0008-0594.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197505
ENTRY DATE: Entered STN: 10 Mar 1990
Last Updated on STN: 10 Mar 1990
Entered Medline: 10 May 1975

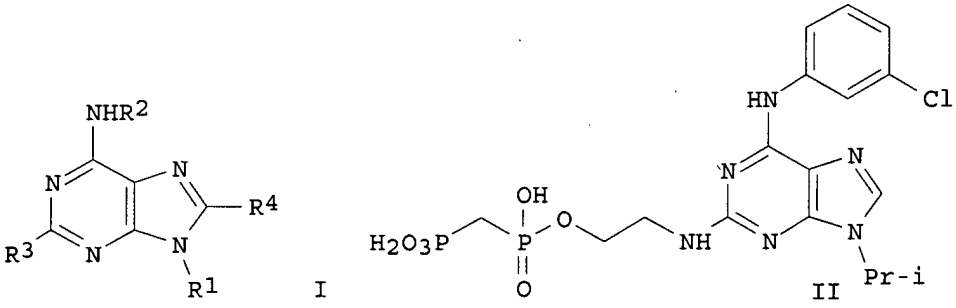
L3 ANSWER 16 OF 16 MEDLINE on STN
ACCESSION NUMBER: 71278365 MEDLINE
DOCUMENT NUMBER: PubMed ID: 4327776
TITLE: Role of adenosine-3',5'-monophosphate in the hormonal regulation of bone resorption: studies with cultured fetal bone.
AUTHOR: Klein D C; Raisz L G
SOURCE: Endocrinology, (1971 Sep) Vol. 89, No. 3, pp. 818-26.
Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: (IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 197110
ENTRY DATE: Entered STN: 1 Jan 1990
Last Updated on STN: 1 Jan 1990
Entered Medline: 28 Oct 1971

ANSWER 1 OF 1 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2002:429543 CAPLUS
DOCUMENT NUMBER: 137:6038
TITLE: Preparation of purine derivatives as bone resorption inhibitors
INVENTOR(S): Weigele, Manfred; Sawyer, Tomi K.; Bohacek, Regine; Shakespeare, William C.; Sundaramoorthi, Rajeswari; Wang, Yihan; Dalgarno, David C.; Metcalf, Chester A.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 99 pp., Cont.-in-part of U.S. Ser. No. 740,267.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2002068721	A1	20020606	US 2000-740393		20001218
US 7115589	B2	20061003			
US 2002103161	A1	20020801	US 2000-740267		20001218
US 2002132819	A1	20020919	US 2000-740653		20001218
AT 327242	T	20060615	AT 2000-986551		20001218
US 2005096298	A1	20050505	US 2004-994962		20041122
PRIORITY APPLN. INFO.:			US 1999-172161P	P	19991217
			US 1999-172510P	P	19991217
			US 2000-240788P	P	20001016
			US 2000-740267	A2	20001218
			US 2000-740653	A2	20001218
			US 2000-740619	A	20001218

OTHER SOURCE(S): MARPAT 137:6038
GI



AB Purine derivs. of formula I [R1 = H, aliphatic, heteroaliph., aryl, or heteroaryl moiety; R2 = aliphatic, heteroaliph., aryl, or heteroaryl moiety; R3, R4 = H, halo, (substituted) OH, (substituted) NH, (substituted) SH, aliphatic, heteroaliph., aryl, or heteroaryl moiety] are prepared for use as bone resorption inhibitors. Thus, II was prepared from 2-amino-6-chloropurine, 2-propanol, 3-chloroaniline, ethanolamine and methylenebis(phosphonic dichloride). The preferred compds. I have IC50 values below 500 nM in the anti-resorption cell assay on white rabbits.

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> d his

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     (FILE 'HOME' ENTERED AT 09:40:56 ON 21 JAN 2008)

     FILE 'CAPLUS, MEDLINE' ENTERED AT 09:41:15 ON 21 JAN 2008
L1            70 S ADENOSINE/TI (P) ARTHRITIS/TI
L2             2 S ADENOSINE/TI (P) BONE LOSS/TI
L3            16 S ADENOSINE/TI (P) BONE RESORPTION/TI
L4             1 S PURINE DERIVATIVES/TI (P) BONE RESORPTION/TI

=> s purine derivativ?/TI (P) bone resorption/TI
L5             1 PURINE DERIVATIV?/TI (P) BONE RESORPTION/TI

=> s purines/TI (P) bone resorption/TI
L6             2 PURINES/TI (P) BONE RESORPTION/TI

=> d L6 1-2 ibib abs

L6   ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:         2003:484513  CAPLUS
DOCUMENT NUMBER:          139:317497
TITLE:                    Regulation of bone resorption and
                          formation by purines and pyrimidines
AUTHOR(S):                Hoebertz, Astrid; Arnett, Timothy R.; Burnstock,
                          Geoffrey
CORPORATE SOURCE:         Research Institute of Molecular Biology, Vienna, 1030,
                          Austria
SOURCE:                   Trends in Pharmacological Sciences (2003), 24(6),
                          290-297
                          CODEN: TPHSDY; ISSN: 0165-6147
PUBLISHER:                Elsevier Science Ltd.
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 English
AB   A review.  Growing evidence suggests that extracellular nucleotides,
     signaling through P2 receptors, might play important roles in the
     regulation of bone and cartilage metabolism  ATP and other nucleotides can
     exert impressive stimulatory effects on the formation and activity of
     osteoclasts (bone-resorbing cells) in addition to inhibiting bone formation
     by osteoblasts.  In this review, the current understanding of the actions
     of nucleotides on skeletal cells and the probable receptor subtypes
     involved are discussed.
REFERENCE COUNT:          60    THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6   ANSWER 2 OF 2     MEDLINE on STN
ACCESSION NUMBER:   2003297487     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 12823955
TITLE:              Regulation of bone resorption and
                    formation by purines and pyrimidines.
AUTHOR:             Hoebertz Astrid; Arnett Timothy R; Burnstock Geoffrey
CORPORATE SOURCE:   Research Institute of Molecular Biology, Dr Bohr Gasse 7,
                    1030 Vienna, Austria.
SOURCE:             Trends in pharmacological sciences, (2003 Jun) Vol. 24, No.
                    6, pp. 290-7.  Ref: 60
                    Journal code: 7906158. ISSN: 0165-6147.
PUB. COUNTRY:       England: United Kingdom
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
                    (RESEARCH SUPPORT, NON-U.S. GOV'T)
                    General Review; (REVIEW)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200308
ENTRY DATE:         Entered STN: 26 Jun 2003
                    Last Updated on STN: 7 Aug 2003
                    Entered Medline: 6 Aug 2003
AB   Growing evidence suggests that extracellular nucleotides, signalling
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through P2 receptors, might play important roles in the regulation of bone and cartilage metabolism. ATP and other nucleotides can exert impressive stimulatory effects on the formation and activity of osteoclasts (bone-resorbing cells) in addition to inhibiting bone formation by osteoblasts. In this review, the current understanding of the actions of nucleotides on skeletal cells and the probable receptor subtypes involved are discussed.

L9 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2003:484513 CAPLUS
DOCUMENT NUMBER: 139:317497
TITLE: Regulation of bone resorption and formation by purines and pyrimidines
AUTHOR(S): Hoebertz, Astrid; Arnett, Timothy R.; Burnstock, Geoffrey
CORPORATE SOURCE: Research Institute of Molecular Biology, Vienna, 1030, Austria
SOURCE: Trends in Pharmacological Sciences (2003), 24(6), 290-297
CODEN: TPHSDY; ISSN: 0165-6147
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Growing evidence suggests that extracellular nucleotides, signaling through P2 receptors, might play important roles in the regulation of bone and cartilage metabolism ATP and other nucleotides can exert impressive stimulatory effects on the formation and activity of osteoclasts (bone-resorbing cells) in addition to inhibiting bone formation by osteoblasts. In this review, the current understanding of the actions of nucleotides on skeletal cells and the probable receptor subtypes involved are discussed.
REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:429543 CAPLUS
DOCUMENT NUMBER: 137:6038
TITLE: Preparation of purine derivatives as bone resorption inhibitors
INVENTOR(S): Weigele, Manfred; Sawyer, Tomi K.; Bohacek, Regine; Shakespeare, William C.; Sundaramoorthi, Rajeswari; Wang, Yihan; Dalgarno, David C.; Metcalf, Chester A.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 99 pp., Cont.-in-part of U.S. Ser. No. 740,267.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2002068721	A1	20020606	US 2000-740393		20001218
US 7115589	B2	20061003			
US 2002103161	A1	20020801	US 2000-740267		20001218
US 2002132819	A1	20020919	US 2000-740653		20001218
AT 327242	T	20060615	AT 2000-986551		20001218
US 2005096298	A1	20050505	US 2004-994962		20041122
PRIORITY APPLN. INFO.:			US 1999-172161P	P	19991217
			US 1999-172510P	P	19991217
			US 2000-240788P	P	20001016
			US 2000-740267	A2	20001218
			US 2000-740653	A2	20001218
			US 2000-740619	A	20001218

OTHER SOURCE(S): MARPAT 137:6038
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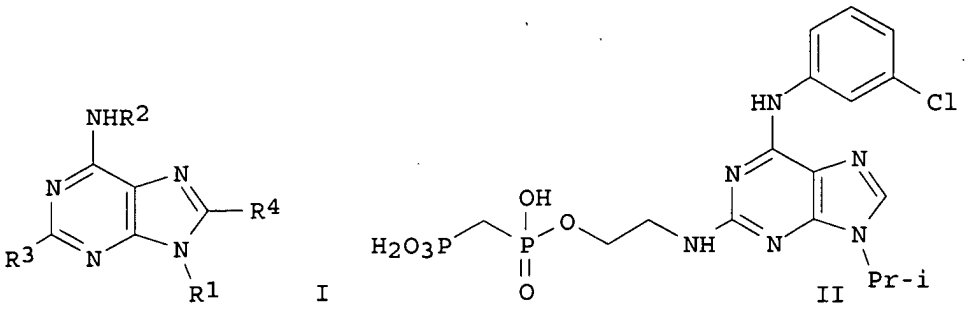


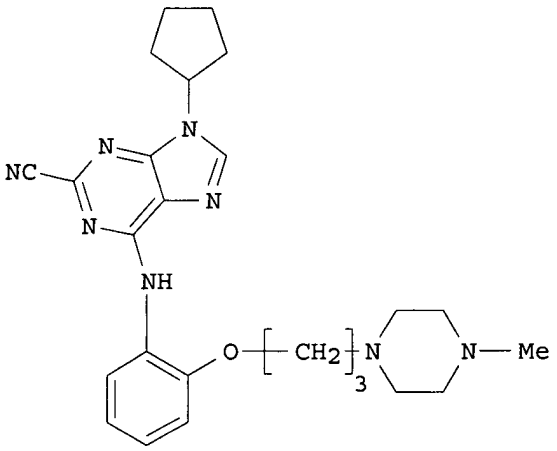
AB Purine derivs. of formula I [R1 = H, aliphatic, heteroaliph., aryl, or heteroaryl moiety; R2 = aliphatic, heteroaliph., aryl, or heteroaryl moiety; R3, R4 = H, halo, (substituted) OH, (substituted) NH, (substituted) SH, aliphatic, heteroaliph., aryl, or heteroaryl moiety] are prepared for use as bone resorption inhibitors. Thus, II was prepared from 2-amino-6-chloropurine, 2-propanol, 3-chloroaniline, ethanolamine and methylenebis(phosphonic dichloride). The preferred compds. I have IC50 values below 500 nM in the anti-resorption cell assay on white rabbits.

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 3 MEDLINE on STN
ACCESSION NUMBER: 2003297487 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12823955
TITLE: Regulation of bone resorption and formation by purines and pyrimidines.
AUTHOR: Hoebertz Astrid; Arnett Timothy R; Burnstock Geoffrey
CORPORATE SOURCE: Research Institute of Molecular Biology, Dr Bohr Gasse 7, 1030 Vienna, Austria.
SOURCE: Trends in pharmacological sciences, (2003 Jun) Vol. 24, No. 6, pp. 290-7. Ref: 60
Journal code: 7906158. ISSN: 0165-6147.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 26 Jun 2003
Last Updated on STN: 7 Aug 2003
Entered Medline: 6 Aug 2003

AB Growing evidence suggests that extracellular nucleotides, signalling through P2 receptors, might play important roles in the regulation of bone and cartilage metabolism. ATP and other nucleotides can exert impressive stimulatory effects on the formation and activity of osteoclasts (bone-resorbing cells) in addition to inhibiting bone formation by osteoblasts. In this review, the current understanding of the actions of nucleotides on skeletal cells and the probable receptor subtypes involved are discussed.

L18 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:886368 CAPLUS
DOCUMENT NUMBER: 141:360213
TITLE: Novel Purine Nitrile Derived Inhibitors of the Cysteine Protease Cathepsin K
AUTHOR(S): Altmann, Eva; Cowan-Jacob, Sandra W.; Missbach, Martin
CORPORATE SOURCE: Novartis Institutes for BioMedical Research, Basel, CH-4002, Switz.
SOURCE: Journal of Medicinal Chemistry (2004), 47(24), 5833-5836
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:360213
GI



I

AB Starting from a high-throughput screening hit, novel cathepsin K inhibitors have been developed based on a purine scaffold. High-resolution X-ray structures of several derivs. have revealed the binding mode of these unique cysteine protease inhibitors.
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2003:862609 CAPLUS
DOCUMENT NUMBER: 140:157794
TITLE: Blockade of the pore-forming P2X7 receptor inhibits formation of multinucleated human osteoclasts in vitro
AUTHOR(S): Gartland, A.; Buckley, K. A.; Bowler, W. B.; Gallagher, J. A.
CORPORATE SOURCE: Department Human Anatomy and Cell Biology, Human Bone Cell Research Group, The University of Liverpool, Liverpool, L69 3GE, UK
SOURCE: Calcified Tissue International (2003), 73(4), 361-369
CODEN: CTINDZ; ISSN: 0171-967X
PUBLISHER: Springer-Verlag New York Inc.

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Osteoclasts are large, multinucleated, terminally differentiated cells formed by the fusion of mononuclear hemopoietic precursors. Their function is the resorption of bone, which is an essential part of the growth, modeling and remodeling of the skeleton. Though some osteoclast differentiation factors have recently been identified, the mol. basis for the fusion process that leads to multinucleation is poorly understood. The ATP-gated P2X7 receptor is a plasma membrane receptor belonging to the family of P2X purinergic receptors. It is known to be expressed by cells of hemopoietic origin where its activation leads to multiple downstream events including cytokine release, cell permeabilization and apoptosis. More recently this receptor has been implicated in the generation of multinucleated giant cells and polykaryons. Here we show that human osteoclasts express P2X7 receptors in vitro and in vivo, and that these receptors are functional in vitro, as assessed by pore-formation studies. More importantly, blockade of the P2X7 receptor with the antagonist oxidized ATP or a blocking monoclonal antibody significantly inhibits the fusion of osteoclast precursors to form multinucleated osteoclasts. Taken in combination with previous results from our laboratory demonstrating P2X7 receptor-mediated apoptosis and inhibition of bone resorption in vitro, these data suggest an important role for the P2X7 receptor in the regulation of the osteoclast population. The P2X7 receptor provides a significant new target for modulating osteoclast function in diseases characterized by increased osteoclast number and excessive bone turnover.
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

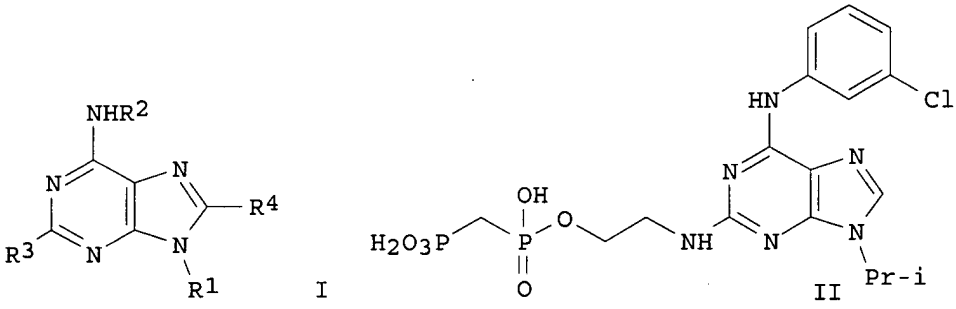
L18 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2003:484513 CAPLUS
DOCUMENT NUMBER: 139:317497
TITLE: Regulation of bone resorption and formation by purines and pyrimidines
AUTHOR(S): Hoebertz, Astrid; Arnett, Timothy R.; Burnstock, Geoffrey
CORPORATE SOURCE: Research Institute of Molecular Biology, Vienna, 1030, Austria
SOURCE: Trends in Pharmacological Sciences (2003), 24(6), 290-297
CODEN: TPHSDY; ISSN: 0165-6147
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Growing evidence suggests that extracellular nucleotides, signaling through P2 receptors, might play important roles in the regulation of bone and cartilage metabolism ATP and other nucleotides can exert impressive stimulatory effects on the formation and activity of osteoclasts (bone-resorbing cells) in addition to inhibiting bone formation by osteoblasts. In this review, the current understanding of the actions of nucleotides on skeletal cells and the probable receptor subtypes involved are discussed.
REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:429543 CAPLUS
DOCUMENT NUMBER: 137:6038
TITLE: Preparation of purine derivatives as bone resorption inhibitors
INVENTOR(S): Weigele, Manfred; Sawyer, Tomi K.; Bohacek, Regine; Shakespeare, William C.; Sundaramoorthi, Rajeswari; Wang, Yihan; Dalgarno, David C.; Metcalf, Chester A.
PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 99 pp., Cont.-in-part of U.S. Ser. No. 740,267.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2002068721	A1	20020606	US 2000-740393		20001218
US 7115589	B2	20061003			
US 2002103161	A1	20020801	US 2000-740267		20001218
US 2002132819	A1	20020919	US 2000-740653		20001218
AT 327242	T	20060615	AT 2000-986551		20001218
US 2005096298	A1	20050505	US 2004-994962		20041122
PRIORITY APPLN. INFO.:			US 1999-172161P	P	19991217
			US 1999-172510P	P	19991217
			US 2000-240788P	P	20001016
			US 2000-740267	A2	20001218
			US 2000-740653	A2	20001218
			US 2000-740619	A	20001218

OTHER SOURCE(S): MARPAT 137:6038
GI



AB Purine derivs. of formula I [R1 = H, aliphatic, heteroaliph., aryl, or heteroaryl moiety; R2 = aliphatic, heteroaliph., aryl, or heteroaryl moiety; R3, R4 = H, halo, (substituted) OH, (substituted) NH, (substituted) SH, aliphatic, heteroaliph., aryl, or heteroaryl moiety] are prepared for use as bone resorption inhibitors. Thus, II was prepared from 2-amino-6-chloropurine, 2-propanol, 3-chloroaniline, ethanolamine and methylenebis(phosphonic dichloride). The preferred compds. I have IC50 values below 500 nM in the anti-resorption cell assay on white rabbits.
REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 11 OF 14 MEDLINE on STN
ACCESSION NUMBER: 2006389205 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16805422
TITLE: Purinergic signalling--an overview.
AUTHOR: Burnstock Geoffrey
CORPORATE SOURCE: Autonomic Neuroscience Centre, Royal Free and University College Medical School, London, UK.
SOURCE: Novartis Foundation symposium, (2006) Vol. 276, pp. 26-48; discussion 48-57, 275-81. Ref: 63
Journal code: 9807767. ISSN: 1528-2511.

PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200608
ENTRY DATE: Entered STN: 30 Jun 2006
Last Updated on STN: 23 Aug 2006
Entered Medline: 22 Aug 2006

AB A brief account of the early history of extracellular signalling by ATP will be followed by a summary of the current subclassification of receptors for purines and pyrimidines. On the basis of cloning, transduction mechanisms and pharmacology, the P1 (adenosine) receptor family has 4 subtypes, while the P2 (ATP, ADP and UTP) receptor family has been divided into P2X ionotropic receptors (7 subtypes) and P2Y metabotropic G protein-coupled receptors (8 subtypes). The distribution of purinoceptors in both neuronal and non-neuronal cells and the physiology and pathophysiology of purinergic signalling will be reviewed. Examples of fast purinergic signalling include cotransmission and neuromodulation, exocrine and endocrine secretion, platelet aggregation, vascular endothelial cell-mediated vasodilatation and nociceptive mechanosensory transduction. Examples of slow (trophic) purinergic signalling include cell proliferation, differentiation and apoptosis in embryological development, neural regeneration, bone resorption, cell turnover of epithelial cells in skin and visceral organs, inflammation, wound healing and cancer. Finally the purinoceptor subtypes expressed on astrocytes, oligodendrocytes, Schwann cells, microglia, Muller cells and enteric glial cells will be summarized as well as evidence for non-lytic release of ATP from glial cells.

L18 ANSWER 12 OF 14 MEDLINE on STN
ACCESSION NUMBER: 2006105822 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16492148
TITLE: Structural basis of Src tyrosine kinase inhibition with a new class of potent and selective trisubstituted purine-based compounds.
AUTHOR: Dalgarno David; Stehle Thilo; Narula Surinder; Schelling Pierre; van Schravendijk Marie Rose; Adams Susan; Andrade Lawrence; Keats Jeff; Ram Mary; Jin Lei; Grossman Trudy; MacNeil Ian; Metcalf Chester 3rd; Shakespeare William; Wang Yihan; Keenan Terry; Sundaramoorthi Raji; Bohacek Regine; Weigele Manfred; Sawyer Tomi
CORPORATE SOURCE: ARIAD Pharmaceuticals, 26 Landsdowne Street, Cambridge, MA 02139, USA.. dalgarno@ariad.com
SOURCE: Chemical biology & drug design, (2006 Jan) Vol. 67, No. 1, pp. 46-57.
Journal code: 101262549. ISSN: 1747-0277.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200607
ENTRY DATE: Entered STN: 23 Feb 2006
Last Updated on STN: 26 Jul 2006
Entered Medline: 25 Jul 2006

AB The tyrosine kinase pp60src (Src) is the prototypical member of a family of proteins that participate in a broad array of cellular signal transduction processes, including cell growth, differentiation, survival, adhesion, and migration. Abnormal Src family kinase (SFK) signaling has been linked to several disease states, including osteoporosis and cancer metastases. Src has thus emerged as a molecular target for the discovery of small-molecule inhibitors that regulate Src kinase activity by binding

to the ATP pocket within the catalytic domain. Here, we present crystal structures of the kinase domain of Src in complex with two purine -based inhibitors: AP23451, a small-molecule inhibitor designed to inhibit Src-dependent bone resorption, and AP23464, a small-molecule inhibitor designed to inhibit the Src-dependent metastatic spread of cancer. In each case, a trisubstituted purine template core was elaborated using structure-based drug design to yield a potent Src kinase inhibitor. These structures represent early examples of high affinity purine-based Src family kinase-inhibitor complexes, and they provide a detailed view of the specific protein-ligand interactions that lead to potent inhibition of Src. In particular, the 3-hydroxyphenethyl N9 substituent of AP23464 forms unique interactions with the protein that are critical to the picomolar affinity of this compound for Src. The comparison of these new structures with two relevant kinase-inhibitor complexes provides a structural basis for the observed kinase inhibitory selectivity. Further comparisons reveal a concerted induced-fit movement between the N- and C-terminal lobes of the kinase that correlates with the affinity of the ligand. Binding of the most potent inhibitor, AP23464, results in the largest induced-fit movement, which can be directly linked to interactions of the hydrophenethyl N9 substituent with a region at the interface between the two lobes. A less pronounced induced-fit movement is also observed in the Src-AP23451 complex. These new structures illustrate how the combination of structural, computational, and medicinal chemistry can be used to rationalize the process of developing high affinity, selective tyrosine kinase inhibitors as potential therapeutic agents.

L18 ANSWER 13 OF 14 MEDLINE on STN
ACCESSION NUMBER: 2004036986 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12874700
TITLE: Blockade of the pore-forming P2X7 receptor inhibits formation of multinucleated human osteoclasts in vitro.
AUTHOR: Gartland A; Buckley K A; Bowler W B; Gallagher J A
CORPORATE SOURCE: Human Bone Cell Research Group, Department Human Anatomy and Cell Biology, The University of Liverpool, Liverpool, L69 3GE, UK. Alison.Gartland@ umassmed.edu.
SOURCE: Calcified tissue international, (2003 Oct) Vol. 73, No. 4, pp. 361-9. Electronic Publication: 2003-07-24. Journal code: 7905481. ISSN: 0171-967X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200406
ENTRY DATE: Entered STN: 23 Jan 2004
Last Updated on STN: 29 Jun 2004
Entered Medline: 28 Jun 2004

AB Osteoclasts are large, multinucleated, terminally differentiated cells formed by the fusion of mononuclear hemopoietic precursors. Their function is the resorption of bone, which is an essential part of the growth, modeling and remodeling of the skeleton. Though some osteoclast differentiation factors have recently been identified, the molecular basis for the fusion process that leads to multinucleation is poorly understood. The ATP-gated P2X7 receptor is a plasma membrane receptor belonging to the family of P2X purinergic receptors. It is known to be expressed by cells of hemopoietic origin where its activation leads to multiple downstream events including cytokine release, cell permeabilization and apoptosis. More recently this receptor has been implicated in the generation of multinucleated giant cells and polykaryons. Here we show that human osteoclasts express P2X7 receptors in vitro and in vivo, and that these receptors are functional in vitro, as assessed by pore-formation studies. More importantly, blockade of the P2X7 receptor with the antagonist oxidized ATP or a blocking monoclonal antibody

significantly inhibits the fusion of osteoclast precursors to form multinucleated osteoclasts. Taken in combination with previous results from our laboratory demonstrating P2X7 receptor-mediated apoptosis and inhibition of bone resorption in vitro, these data suggest an important role for the P2X7 receptor in the regulation of the osteoclast population. The P2X7 receptor provides a significant new target for modulating osteoclast function in diseases characterized by increased osteoclast number and excessive bone turnover.

L18 ANSWER 14 OF 14 MEDLINE on STN
ACCESSION NUMBER: 2003297487 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12823955
TITLE: Regulation of bone resorption and formation by purines and pyrimidines.
AUTHOR: Hoebertz Astrid; Arnett Timothy R; Burnstock Geoffrey
CORPORATE SOURCE: Research Institute of Molecular Biology, Dr Bohr Gasse 7, 1030 Vienna, Austria.
SOURCE: Trends in pharmacological sciences, (2003 Jun) Vol. 24, No. 6, pp. 290-7. Ref: 60
Journal code: 7906158. ISSN: 0165-6147.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 26 Jun 2003
Last Updated on STN: 7 Aug 2003
Entered Medline: 6 Aug 2003

AB Growing evidence suggests that extracellular nucleotides, signalling through P2 receptors, might play important roles in the regulation of bone and cartilage metabolism. ATP and other nucleotides can exert impressive stimulatory effects on the formation and activity of osteoclasts (bone-resorbing cells) in addition to inhibiting bone formation by osteoblasts. In this review, the current understanding of the actions of nucleotides on skeletal cells and the probable receptor subtypes involved are discussed.

L9 ANSWER 10 OF 26 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:493743 CAPLUS
DOCUMENT NUMBER: 141:47836
TITLE: Cloning and characterization of INSP101, a splice variant of the human pituitary growth hormone, and diagnostic and therapeutic uses thereof
INVENTOR(S): Fagan, Richard Joseph; Phelps, Christopher Benjamin; Rodrigues, Tania Maria; Yorke, Melanie; De Tiani, Mariastella
PATENT ASSIGNEE(S): Ares Trading S.A., Switz.
SOURCE: PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004050703	A1	20040617	WO 2003-GB5295		20031205
WO 2004050703	A8	20040923			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2507631	A1	20040617	CA 2003-2507631		20031205
AU 2003285589	A1	20040623	AU 2003-285589		20031205
EP 1569961	A1	20050907	EP 2003-778588		20031205
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
JP 2006525782	T	20061116	JP 2004-556543		20031205
NO 2005002525	A	20050816	NO 2005-2525		20050526
US 2006275293	A1	20061207	US 2005-537142		20051110
PRIORITY APPLN. INFO.:			GB 2002-28441	A	20021205
			WO 2003-GB5295	W	20031205

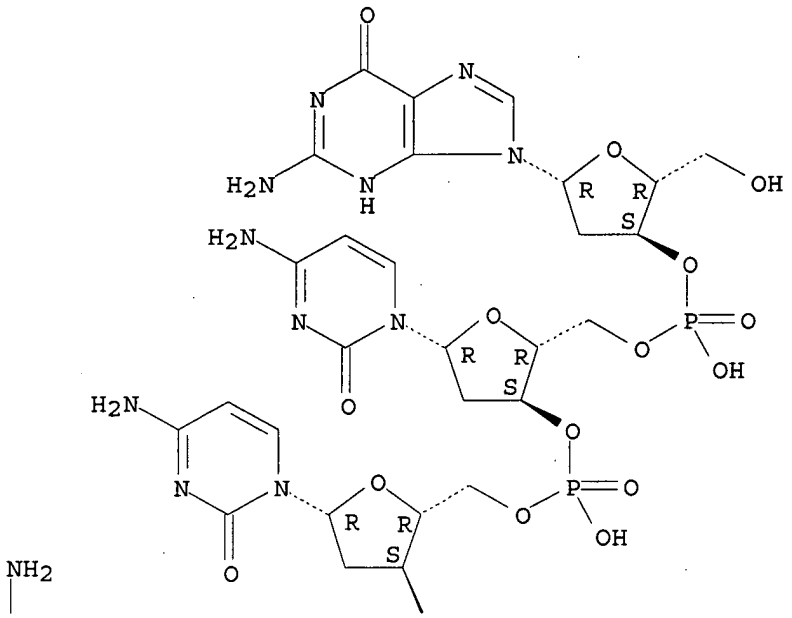
AB This invention relates to a novel protein, termed INSP101, herein identified as a novel splice variant of human pituitary growth hormone and to the use of this protein and nucleic acid sequence from the encoding genes in the diagnosis, prevention and treatment of disease. Cloning strategy, structure-activity studies and characterization of INSP101 are exemplified.

IT 248256-68-0
RL: PRP (Properties)
(unclaimed sequence; cloning and characterization of INSP101, a splice variant of the human pituitary growth hormone, and diagnostic and therapeutic uses thereof)

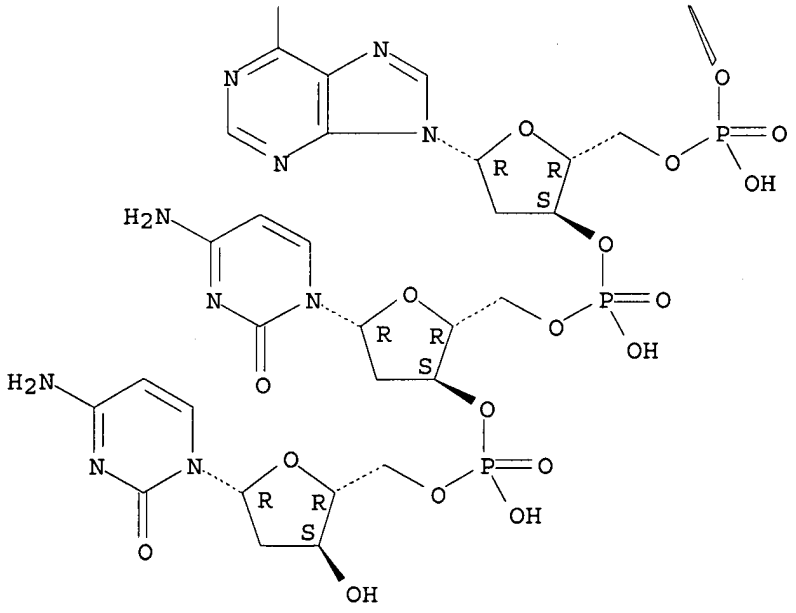
RN 248256-68-0 CAPLUS
CN Cytidine, 2'-deoxyguanylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxyadenylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 11 OF 26 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:452977 CAPLUS
DOCUMENT NUMBER: 141:17599
TITLE: Integrin peptide-polymer bioconjugates that block cell interactions and have anti-inflammatory and immunosuppressant activities
INVENTOR(S): Massia, Stephen P.; Ehteshami, Ghola Reza

PATENT ASSIGNEE(S): Arizona Board of Regents Arizona State University, USA
SOURCE: PCT Int. Appl., 253 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004045542	A2	20040603	WO 2003-US36763	20031117
WO 2004045542	A3	20041021		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003294318	A1	20040615	AU 2003-294318	20031117
EP 1570270	A2	20050907	EP 2003-789801	20031117
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

PRIORITY APPLN. INFO.: US 2002-295734 A 20021115
WO 2003-US36763 W 20031117

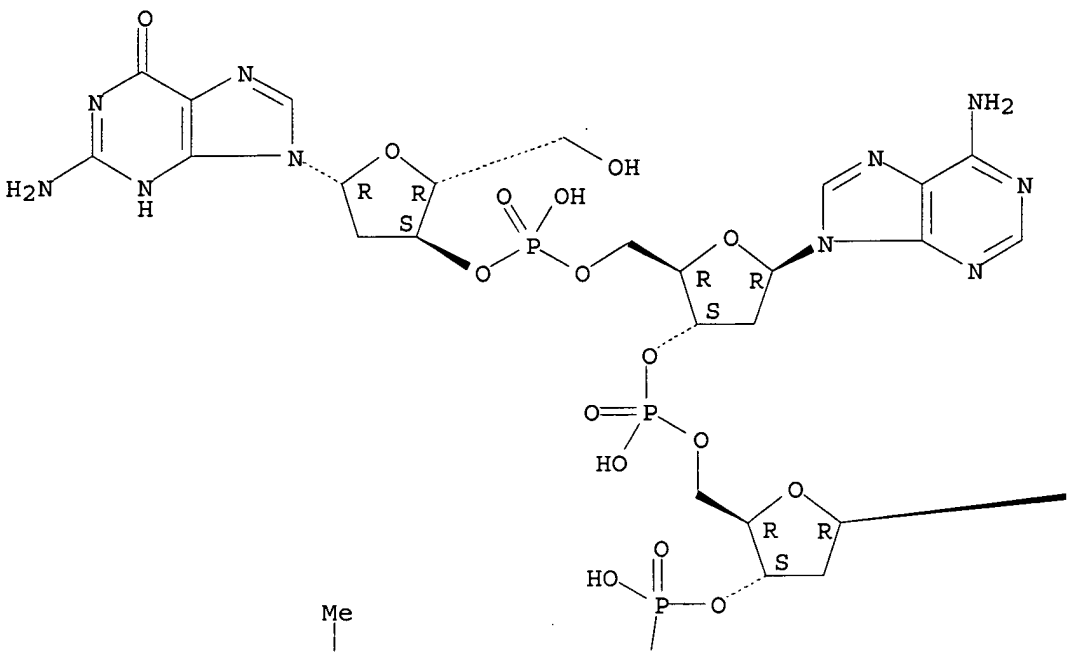
AB The invention claims therapeutic bioconjugates composed of hydrophilic polymers covalently bound to one or more peptides capable of binding specifically to a ligand expressed on a cell surface. The integrin peptide-polymer bioconjugates prevent attachment of cells with the binding partner of the ligand. In an example of the invention, adhesion of human monocytes to tumor necrosis factor α-stimulated, ICAM-expressing bovine endothelial cells was blocked by a CD11B/CD18 agonist (active peptide/dextran).

IT 68211-64-3
RL: PRP (Properties)
(unclaimed sequence; integrin peptide-polymer bioconjugates that block cell interactions and have anti-inflammatory and immunosuppressant activities)

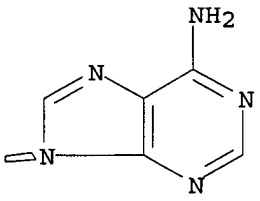
RN 68211-64-3 CAPLUS
CN Thymidine, 2'-deoxyguanylyl-(3'→5')-2'-deoxyadenylyl-(3'→5')-2'-deoxyadenylyl-(3'→5')-thymidylyl-(3'→5')-2'-deoxyadenylyl-(3'→5')- (9CI) (CA INDEX NAME)

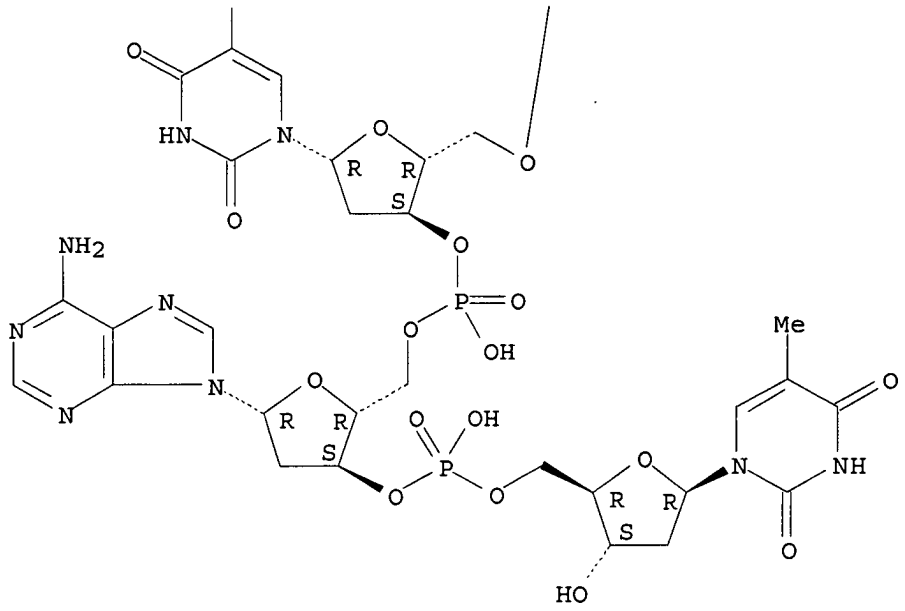
Absolute stereochemistry.

PAGE 1-A



PAGE 1-B





L9 ANSWER 12 OF 26 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2003:208816 CAPLUS
DOCUMENT NUMBER: 139:270558
TITLE: Effects of cyclosporine on osteoclast activity: inhibition of calcineurin activity with minimal effects on bone resorption and acid transport activity
AUTHOR(S): Williams, John P.; McKenna, Margaret A.; Thames, Allyn M., III; McDonald, Jay M.
CORPORATE SOURCE: Department of Internal Medicine, Division of Nephrology, Bone and Mineral Metabolism, Lexington Veterans Administration Medical Center, University of Kentucky, Lexington, KY, USA
SOURCE: Journal of Bone and Mineral Research (2003), 18(3), 451-457
CODEN: JBMREJ; ISSN: 0884-0431
PUBLISHER: American Society for Bone and Mineral Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cyclosporine results in rapid and profound bone loss in transplant patients, an effect ascribed to osteoclasts. Cyclosporine, complexed with the appropriate immunophilin, inhibits calcineurin (the calcium/calmodulin dependent serine/threonine phosphatase) activity. We tested the hypothesis that cyclosporine inhibits calcineurin activity in osteoclasts, resulting in stimulation of osteoclast activity. We compared the effects of cyclosporine A and the calmodulin antagonist, tamoxifen, on bone resorption by avian osteoclasts. Tamoxifen inhibits bone resorption .apprx.60%, whereas cyclosporine A only inhibited bone resorption 12%. One-hour treatment with 100 nM cyclosporine inhibited osteoclast calcineurin activity 70% in whole cell lysates, whereas 10 μM tamoxifen only inhibited calcineurin activity 25%. We compared the effects of cyclosporine A and tamoxifen on acid transport activity in isolated membrane vesicles and in isolated membrane vesicles obtained from osteoclasts treated with cyclosporine A or tamoxifen under conditions that inhibit calcineurin activity. Direct addition of cyclosporine A in the acid transport assay, or pretreatment of cells with cyclosporine A followed by membrane isolation, had no effect on acid transport activity in membrane vesicles. In contrast, direct addition of tamoxifen to membranes inhibits

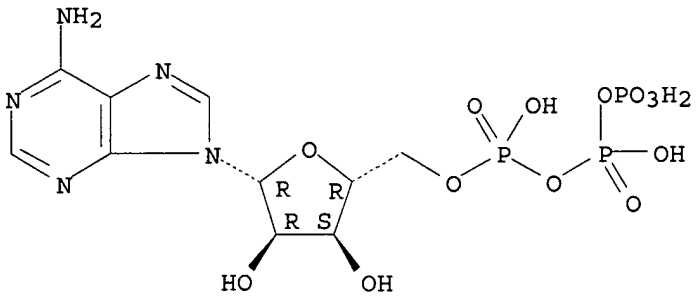
acid transport activity, an effect that can be prevented by addition of exogenous calmodulin. Furthermore, acid transport activity was also inhibited in membrane vesicles isolated from cells treated with tamoxifen. In conclusion, cyclosporine A inhibits osteoclast calcineurin activity; however, calcineurin inhibition does not correspond to a significant effect on acid transport activity in isolated membrane vesicles or bone resorption by osteoclasts.

IT 56-65-5, 5'-ATP, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(effects of cyclosporine and tamoxifen on osteoclast activity in relation to calcineurin activity, bone resorption, and ATP-dependent acid transport activity)

RN 56-65-5 CAPLUS

CN Adenosine 5'-(tetrahydrogen triphosphate) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 13 OF 26 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2002:335701 CAPLUS

DOCUMENT NUMBER: 137:288947

TITLE: Further insight into mechanism of action of clodronate: inhibition of mitochondrial ADP/ATP translocase by a nonhydrolyzable, adenine-containing metabolite

AUTHOR(S): Lehenkari, Petri P.; Kellinsalmi, Maarit; Napankangas, Juha P.; Ylitalo, Kari V.; Monkkonen, Jukka; Rogers, Michael J.; Azhayev, Alex; Vaananen, H. Kalervo; Hassinen, Ilmo E.

CORPORATE SOURCE: Department of Surgery, University of Oulu, Oulu, Finland

SOURCE: Molecular Pharmacology (2002), 61(5), 1255-1262
CODEN: MOPMA3; ISSN: 0026-895X

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Bisphosphonates can be divided into two groups with distinct mol. mechanisms of action depending on the nature of the R2 side chain. Alendronate, like other N-containing bisphosphonates, inhibits bone resorption and causes apoptosis of osteoclasts and other cells in vitro by preventing post-translational modification of GTP-binding proteins with isoprenoid lipids. Clodronate, a bisphosphonate that lacks a N, does not inhibit protein isoprenylation but can be metabolized intracellularly to a β-γ-methylene (AppCp-type) analog of ATP, which is cytotoxic to macrophages in vitro. The detailed mol. basis for the cytotoxic effects of adenosine-5'-[β,γ-dichloromethylene]triphosphate (AppCCl2p) has not been determined yet. This question was addressed by studying the effects of alendronate, clodronate,

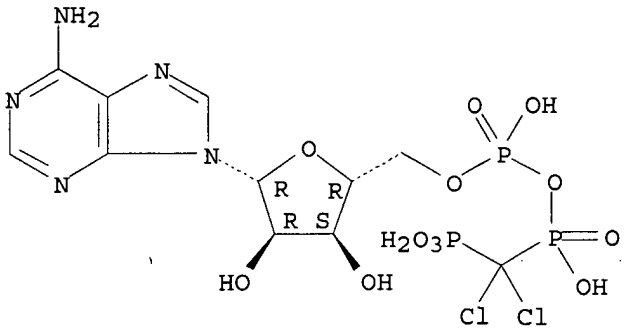
and the clodronate metabolite AppCCl2p on isolated rat liver mitochondria and mitochondrial fractions, and on mitochondrial membrane potential in isolated human osteoclasts. AppCCl2p inhibited mitochondrial O consumption by a mechanism that involves competitive inhibition of the ADP/ATP translocase. Alendronate or the native form of clodronate did not have any immediate effect on mitochondria. However, longer treatment with liposome-encapsulated clodronate caused collapse of the mitochondrial membrane potential, although prominent apoptosis was a late event. Hence, inhibition of the ADP/ATP translocase by the metabolite AppCCl2p is a likely route by which clodronate causes osteoclast apoptosis and inhibits bone resorption.

IT 81336-74-5
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); BIOL (Biological study)
(clodronate metabolite inhibition of mitochondrial ADP/ATP translocase as mechanism of inhibiting bone resorption)

RN 81336-74-5 CAPLUS

CN 5'-Adenylic acid, anhydride with (dichloromethylene)bis[phosphonic acid] (1:1) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 14 OF 26 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2000:685489 CAPLUS

DOCUMENT NUMBER: 134:13563

TITLE: Regulation of collagenase-3 gene expression in osteoblastic and non-osteoblastic cell lines

AUTHOR(S): Selvamurugan, Nagarajan; Brown, Regina J.; Partridge, Nicola C.

CORPORATE SOURCE: Department of Pharmacological and Physiological Science, Saint Louis University School of Medicine, St. Louis, MO, 63104, USA

SOURCE: Journal of Cellular Biochemistry (2000), 79(2), 182-190
CODEN: JCEBD5; ISSN: 0730-2312

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

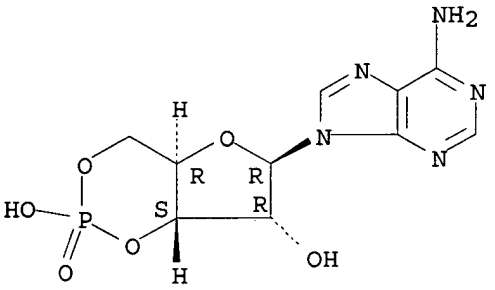
AB Collagenase-3 expression in osteoblastic (UMR 106-01, ROS 17/2.8) and non-osteoblastic cell lines (BC1, NIH3T3) was examined The authors observed that parathyroid hormone (PTH) induces collagenase-3 expression only in UMR cells but not in BC1 (which express collagenase-3 constitutively) or ROS and NIH3T3 cells. Since the authors know from UMR cells that the AP-1 factors and Cbfa1 are required for collagenase-3 expression, they analyzed the expression and PTH regulation of these factors by gel shift and Northern blot anal. in all cell lines. Gel mobility shift with a [32P]-labeled collagenase-3 AP-1 site probe indicated the induction of

c-Fos in osteoblastic cells upon PTH treatment. While c-fos was induced in UMR cells, both c-fos and jun B were induced in ROS cells. Since Jun B is inhibitory of Fos and Jun in the regulation of the rat collagenase-3 gene in UMR cells, it is likely that high levels of Jun B prevent PTH stimulation of collagenase-3 in ROS cells. When the authors carried out gel shift anal. with a [32P]-labeled collagenase-3 RD (runt domain) site probe and Northern blot anal. with a Cbfa1 specific probe, they observed the presence of Cbfa1 in both osteoblastic and non-osteoblastic cell lines, but there was no change in the levels of Cbfa1 RNA or protein in these cells under either control conditions or PTH treatment. From the studies described above, it is evident that the expression of collagenase-3 and its regulation by PTH in osteoblastic and non-osteoblastic cells may be influenced by differential temporal stimulation of the AP-1 family members, especially c-Fos and Jun B along with the potential for posttranslational modification(s) of Cbfa1.

IT 60-92-4, CAMP
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(parathormone regulation of collagenase expression in osteoblastic and non-osteoblastic cell lines and AP-1 factors and Cbfa1 involvement in mechanisms thereof)

RN 60-92-4 CAPLUS
CN Adenosine, cyclic 3',5'-(hydrogen phosphate) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 15 OF 26 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1996:234317 CAPLUS
DOCUMENT NUMBER: 124:307154
TITLE: Modulation of adhesion-dependent cAMP signaling by echistatin and alendronate
AUTHOR(S): Fong, Jenny Hwai-Jen; Ingber, Donald E.
CORPORATE SOURCE: Dep. Surgery Pathol., Child. Hosp. & Harvard Med. Sch., Boston, MA, 02115, USA
SOURCE: Biochemical and Biophysical Research Communications (1996), 221(1), 19-24
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We measured intracellular cAMP levels in cells during attachment and spreading on different extracellular matrix (ECM) proteins. Increases in cAMP were observed within minutes when cells attached to fibronectin, vitronectin, and a synthetic RGD-containing fibronectin peptide (Petite 2000), but not when they adhered to another integrin αvβ3 ligand, echistatin. Because echistatin also inhibits bone resorption, we measured the effects of adding another osteoporosis inhibitor, alendronate, in this system. Alendronate inhibited the cAMP increase induced by ligands that primarily utilize integrin

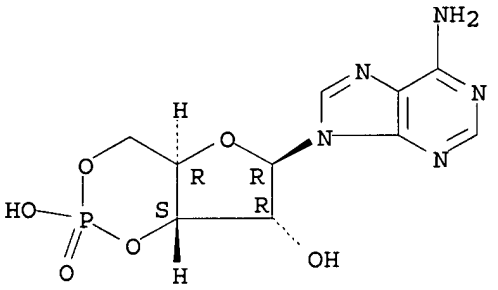
αvβ3 (vitronectin, Peptite 2000), but not by fibronectin which can also use integrin α5β1. These results show that cell adhesion to ECM can increase intracellular cAMP levels and raise the possibility that inhibitors of osteoporosis may act, in part, by preventing activation of this pathway by integrins.

IT 60-92-4, CAMP
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(modulation of adhesion-dependent cAMP signaling by echistatin and alendronate)

RN 60-92-4 CAPLUS

CN Adenosine, cyclic 3',5'-(hydrogen phosphate) (CA INDEX NAME)

Absolute stereochemistry.



L9 ANSWER 16 OF 26 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1994:645126 CAPLUS

DOCUMENT NUMBER: 121:245126

TITLE: Inhibitory effects of bisphosphonates on growth of ameba of the cellular slime mold Dictyostelium discoideum

AUTHOR(S): Rogers, Michael J.; Watts, Donald J.; Russell, R. Graham G.; Ji, Xiaohui; Xiong, Xiaojuan; Blackburn, G. Michael; Bayless, Allan V.; Ebetino, Frank H.

CORPORATE SOURCE: Dep. Mol. Biol. Biotechnol., Univ. Sheffield, Sheffield, UK

SOURCE: Journal of Bone and Mineral Research (1994), 9(7), 1029-39
CODEN: JBMREJ; ISSN: 0884-0431

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Bisphosphonates are inhibitors of bone resorption and are used increasingly as therapeutic agents for treating clin. disorders of skeletal metabolism Their mode of action is still not fully understood. The demonstration that methylenebisphosphonate, a simple methylene analog of pyrophosphate, inhibits the axenic growth of amoebae of the slime mold Dictyostelium discoideum and is incorporated into adenine nucleotides suggested that this organism might be useful in elucidating the cellular effects of bisphosphonates. We examined 24 bisphosphonates, including all those of clin. interest as inhibitors of osteoclast-mediated bone resorption in vivo, for their effects on D. discoideum. All the geminal bisphosphonates inhibited growth of Dictyostelium, although the effectiveness of individual compds. varied widely. When the bisphosphonates were ranked there was a remarkable similarity between the order of potency as inhibitors of growth of Dictyostelium and the order of potency as inhibitors of bone resorption. Thus, bisphosphonates with more complex side-chain structures, especially those containing a nitrogen group, were more potent than simple substituted bisphosphonates, some inhibiting Dictyostelium growth even at concns. below 10 μM. It therefore appears that the mechanism by which

bisphosphonates prevent Dictyostelium growth could be similar to the mechanism by which these compds. affect the activity of osteoclasts. Because the mechanisms of action of bisphosphonates on osteoclasts remains unclear, Dictyostelium may provide an addnl. model for studying the biochem. mode of action of bisphosphonates. Furthermore, these studies suggest that Dictyostelium may also be a convenient organism for rapid evaluation of potentially active bisphosphonates.

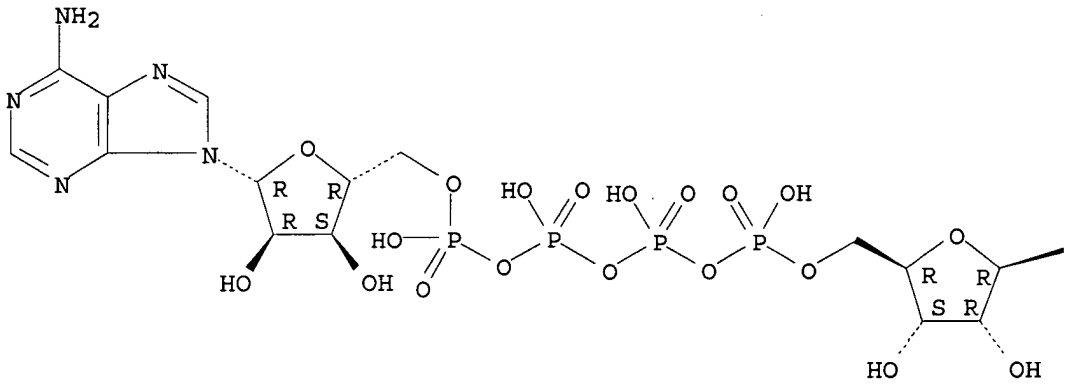
IT 5542-28-9
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(inhibitory effects of bisphosphonates on growth of ameba of cellular slime mold Dictyostelium discoideum for screening of osteoporosis-inhibiting actions)

RN 5542-28-9 CAPLUS

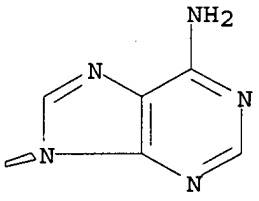
CN Adenosine 5'-(pentahydrogen tetraphosphate), P'''→5'-ester with adenosine (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



L9 ANSWER 17 OF 26 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1994:321173 CAPLUS

DOCUMENT NUMBER: 120:321173

TITLE: Interleukin-4 inhibits bone resorption and acutely increases cytosolic Ca2+ in murine osteoclasts

AUTHOR(S): Bizzarri, Cinzia; Shioi, Atsushi; Teitelbaum, Steven L.; Ohara, Jun-ichi; Harwalkar, Vijay A.; Erdmann, Jeanne M.; Lacey, David L.; Civitelli, Roberto

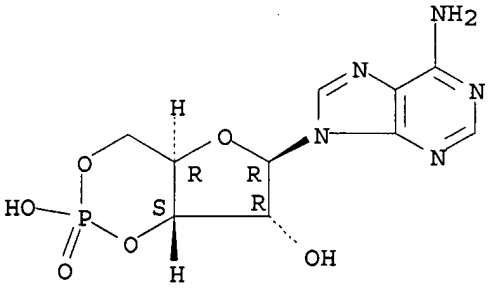
CORPORATE SOURCE: Jewich Hosp., Washington Univ., St. Louis, MO, 63110,

USA
SOURCE: Journal of Biological Chemistry (1994), 269(19), 13817-24
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Interleukin-4 (IL-4) is an immune cytokine recently shown to inhibit bone resorption. To determine whether IL-4 directly acts on osteoclasts, the authors have analyzed its effect on cytosolic calcium concentration [Ca2+]i and bone resorptive function of murine osteoclastic cells generated from bone marrow/stromal cell co-cultures. IL-4 exposure induced an immediate and sustained increase in [Ca2+]i that remained elevated for at least 10 min. This IL-4 effect was dose-dependent, with the maximal effect (209% of baseline) at 200 U/mL and an apparent ED0.5 of 60 U/mL. The IL-4-induced [Ca2+]i rise required extracellular Ca2+ influx, since the response was prevented by LaCl3, and voltage-gated Ca2+ channel blockers, although the IL-4 effect was more sensitive to nicardipine and nifedipine than to diltiazem. Depolarization by high extracellular K+ concentration also raised [Ca2+]i and, under these conditions, osteoclasts failed to respond to IL-4. When intracellular Ca2+ stores were depleted by thapsigargin, IL-4 still induced an increase in [Ca2+]i, although smaller in amplitude and transient. Calcitonin also produced [Ca2+]i increases is osteoclasts, yet it only slightly desensitized these cells to IL-4. Furthermore, IL-4 was much less effective on osteoclasts pretreated (5-10 min) with either forskolin or 8-bromo-cAMP. Both IL-4 and calcitonin were effective even when [Ca2+]i had been increased by exposure to high extracellular Ca2+. Finally, IL-4 dose dependently inhibited the bone-resorptive activity of mature osteoclasts. Therefore, IL-4 signal transduction in osteoclasts involves a rapid and sustained elevation of [Ca2+]i mediated by a voltage-dependent Ca2+ influx, in combination with Ca2+ release from intracellular stores. Modulation of osteoclast [Ca2+]i represents a potential mechanism by which IL-4 inhibits bone resorption.

IT 60-92-4, CAMP
RL: BIOL (Biological study)
(interleukin-4 inhibition of bone resorption by osteoclasts regulation by, signal transduction in relation to)
RN 60-92-4 CAPLUS
CN Adenosine, cyclic 3',5'-(hydrogen phosphate) (CA INDEX NAME)

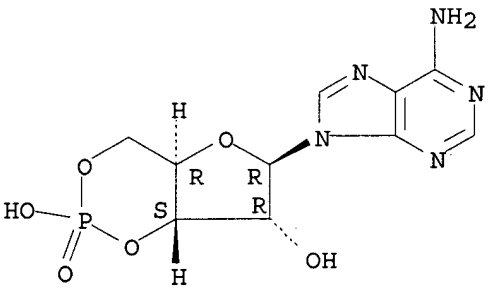
Absolute stereochemistry.



L9 ANSWER 18 OF 26 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1990:509690 CAPLUS
DOCUMENT NUMBER: 113:109690
TITLE: Evidence that the action of calcitonin on rat osteoclasts is mediated by two G proteins acting via separate post-receptor pathways
AUTHOR(S): Zaidi, M.; Datta, H. K.; Moonga, B. S.; MacIntyre, I.
CORPORATE SOURCE: Med. Sch., St. George's Hosp., London, SW17 0RE, UK
SOURCE: Journal of Endocrinology (1990), 126(3), 473-81

CODEN: JOENAK; ISSN: 0022-0795
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Calcitonin inhibits osteoclastic bone resorption, and its action involves 2 sep. acute effects on the osteoclast, both essential to the action of the hormone: abolition of cell motility (Q) and marked cellular retraction (R). The former was mimicked by dibutyryl cAMP and cholera toxin and the latter by pertussis toxin, ionomycin, and increases in ambient Ca. Aluminum fluoride ions produced both Q and R effects, whereas Li prevented both. In addition, calcitonin elicited a biphasic elevation of cytosolic-free Ca in single isolated osteoclasts. It was proposed that the action of calcitonin is mediated by at least 2 G proteins, one responsible for the Q effect and the other for the R effect. In addition, 2nd messengers, cAMP and Ca, are involved. These findings may help to explain the potency of calcitonin in inhibiting bone resorption and may allow the rational design of new therapeutic agents designed to alter osteoclast behavior.
IT 60-92-4, Cyclic AMP
RL: BIOL (Biological study)
(of osteoclast, calcitonin increase of, inhibition of bone resorbing activity mediation by)
RN 60-92-4 CAPLUS
CN Adenosine, cyclic 3',5'-(hydrogen phosphate) (CA INDEX NAME)

Absolute stereochemistry.



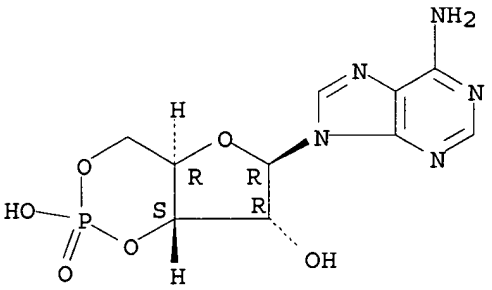
L9 ANSWER 19 OF 26 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1985:162003 CAPLUS
DOCUMENT NUMBER: 102:162003
ORIGINAL REFERENCE NO.: 102:25401a,25404a
TITLE: Direct effects of ethanol on bone resorption and formation in vitro
AUTHOR(S): Farley, J. R.; Fitzsimmons, R.; Taylor, A. K.; Jorch, U. M.; Lau, K. H. W.
CORPORATE SOURCE: Dep. Biochem., Loma Linda Univ., Loma Linda, CA, 92357, USA
SOURCE: Archives of Biochemistry and Biophysics (1985), 238(1), 305-14
CODEN: ABBIA4; ISSN: 0003-9861
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Bone resorption was increased when embryonic chick tibiae were exposed to EtOH [64-17-5] at 0.03-0.3% (volume/volume) and bone formation was inhibited when tibiae were exposed to 0.2% EtOH in the presence of NaF or parathyroid hormone [9002-64-6]. EtOH also had direct effects on isolated bone cells in vitro, increasing both cAMP [60-92-4] and PGE2 [363-24-6] production, and affecting cell proliferation in a biphasic, time- and dose-dependent manner. After 24-h exposure, 0.03% EtOH increased bone cell proliferation, but 0.3% EtOH was inhibitory. Paradoxically, mitogenic doses of EtOH prevented the effects of 2 other mitogens, NaF and human skeletal growth factor, to

increase bone cell proliferation. These direct effects of EtOH on skeletal tissues in vitro may be mediated by changes in bone cell membrane fluidity. DMSO [67-68-5], ethylene glycol [107-21-1], and lecithin, which act, like EtOH, to increase membrane fluidity, mimicked the effects of EtOH on bone cell proliferation. DMSO also mimicked the effect of EtOH to increase cAMP. Cholesterol [57-88-5], which decreases cell membrane fluidity, acted oppositely to EtOH and enhanced the mitogenic response to human skeletal growth factor. Preincubation of calvarial cells with EtOH or with cholesterol altered the in situ reaction kinetics of the membrane-bound enzyme, alkaline phosphatase [9001-78-9]. Together, these data demonstrate that EtOH has direct effects on skeletal tissue in vitro, and suggest that those effects may be secondary to changes in bone cell membrane fluidity.

IT 60-92-4
RL: FORM (Formation, nonpreparative)
(formation of, by bone cells, ethanol effect on)

RN 60-92-4 CAPLUS
CN Adenosine, cyclic 3',5'-(hydrogen phosphate) (CA INDEX NAME)

Absolute stereochemistry.



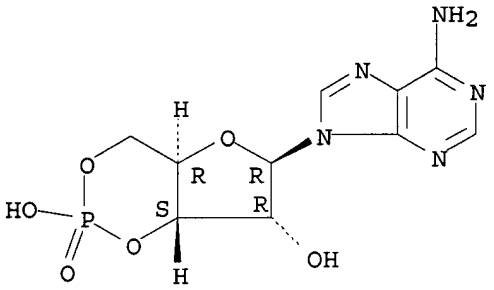
L9 ANSWER 20 OF 26 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1985:76482 CAPLUS
DOCUMENT NUMBER: 102:76482
ORIGINAL REFERENCE NO.: 102:11959a,11962a
TITLE: Cationic agonists and antagonists of bone resorption
AUTHOR(S): Stern, Paula H.
CORPORATE SOURCE: Med. Dent. Sch., Northwestern Univ., Chicago, IL, USA
SOURCE: International Congress Series (1984), 619(Endocr. Control Bone Calcium Metab., Vol. 8A), 109-12
CODEN: EXMDA4; ISSN: 0531-5131
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Ba2+, Co2+, and Mn2+ were tested for their effects on the resorption of fetal rat limb bones and neonatal mouse calvaria. Ba2+ (0.1-1.0 mM) stimulated resorption and potentiated the effects of parathormone (PTH) and 1,25-dihydroxyvitamin D3 (D3) in both limb bones and calvaria. Co2+, at 0.2 mM in limb bones and 1 mM in calvaria, inhibited bone resorption elicited by PTH and D3. Mn2+ produced dose-dependent biphasic effects in both bone and calvaria cultures. It stimulated resorption in bone at 3 μM-0.3 mM and inhibited it at 1 mM. In calvaria, 1 mM Mn2+ was stimulatory after 24 h, but inhibitory after 72 h. Inhibitory concns. of Co2+ and Mn2+ prevented PTH-induced β-glucuronidase release in bone cultures; Mn2+ also inhibited PTH-induced cAMP release. The observations are consistent with the presence of a Ca2+-dependent process in bone resorption . The different dose-response curves with Mn2+ in limb bones and calvaria may indicate different pathways of resorption or factors modulating resorption in these 2 tissues.

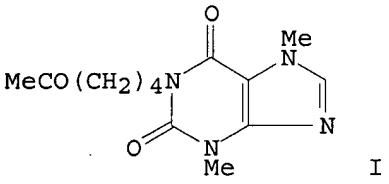
IT 60-92-4

RL: BIOL (Biological study)
(release of, from bone, parathormone stimulation of, manganese inhibition of)
RN 60-92-4 CAPLUS
CN Adenosine, cyclic 3',5'-(hydrogen phosphate) (CA INDEX NAME)

Absolute stereochemistry.



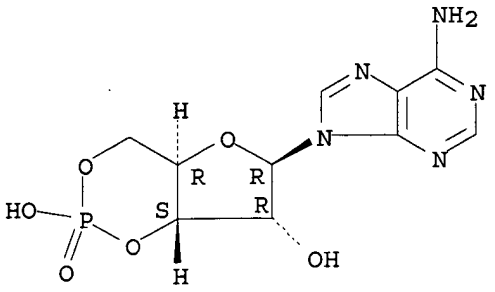
L9 ANSWER 21 OF 26 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1983:516034 CAPLUS
DOCUMENT NUMBER: 99:116034
ORIGINAL REFERENCE NO.: 99:17719a,17722a
TITLE: Studies on osteoporoses. XI. Effects of a methylxanthine derivative
AUTHOR(S): Robin, John C.; Ambrus, Julian L.
CORPORATE SOURCE: Roswell Park Mem. Inst., Buffalo, NY, 14263, USA
SOURCE: Journal of Medicine (Westbury, NY, United States) (1983), 14(2), 137-45
CODEN: JNMDBO; ISSN: 0025-7850
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Pentoxifylline (I) [6493-05-6] (12 mg/kg i.m. twice daily) prevented exptl. osteoporosis in mice. Pentoxifylline (0.1-100 μg/mL) increased Ca2+ uptake and cAMP [60-92-4] production in osteoblast-like bone cells isolated from fetal Sprague-Dawley rats. Theor. implications for osteoblast control of bone resorption are discussed.
IT 60-92-4
RL: FORM (Formation, nonpreparative)
(formation of, in bone cells, pentoxifylline effect on, osteoporosis in relation to)
RN 60-92-4 CAPLUS
CN Adenosine, cyclic 3',5'-(hydrogen phosphate) (CA INDEX NAME)

Absolute stereochemistry.

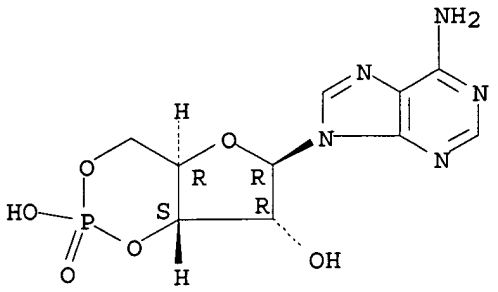


L9 ANSWER 22 OF 26 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1983:515865 CAPLUS
DOCUMENT NUMBER: 99:115865
ORIGINAL REFERENCE NO.: 99:17679a,17682a
TITLE: The effects of dichloromethylene diphosphonate on hypercalcemia and other parameters of the humoral hypercalcemia of malignancy in the rat Leydig cell tumor
AUTHOR(S): Martodam, Raymond R.; Thornton, Kim S.; Sica, Domenic A.; D'Souza, Sharyn M.; Flora, Lawrence; Mundy, Gregory R.
CORPORATE SOURCE: Procter Gamble Co., Cincinnati, OH, USA
SOURCE: Calcified Tissue International (1983), 35(4-5), 512-19
CODEN: CTINDZ; ISSN: 0171-967X
DOCUMENT TYPE: Journal
LANGUAGE: English

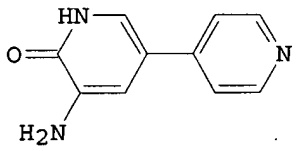
AB The effects of dichloromethylene diphosphonate (I) [10596-23-3] were studied in rats bearing transplantable tumors (Rice D-6) associated with hypercalcemia, hypercalciuria, hypophophatemia, renal phosphate wasting, increased urinary cyclic AMP [60-92-4] excretion, absence of bone metastases, increased osteolclastic bone resorption , and suppressed immunoreactive parathyroid hormone (iPTH) [9002-64-6] concns. Daily administration of I before development of hypercalcemia, in doses from 2.5-40 mg/kg, s.c., delayed and suppressed both the hypercalcemia and hypercalciuria. There was an increase in bone mass and decrease in both osteoclast number and activity compared with bones from untreated tumor-bearing animals. The urinary hydroxyproline excretion in treated animals declined towards the normal range. There were no effects on serum P, urine P, or urine cyclic AMP excretion. These data suggest that I reverses the increased bone resorption that occurs in the humoral hypercalcemia of malignancy and confirm that diphosphonates are effective agents in the prevention and treatment of the increased bone resorption associated with malignant disease. They also suggest that renal phosphate wasting and increased urinary cyclic AMP excretion are not directly related to the hypercalcemia.

IT 60-92-4
RL: BIOL (Biological study)
(urinary excretion of, in neoplasm-associated hypercalcemia, dichloromethylene diphosphonate effect on)
RN 60-92-4 CAPLUS
CN Adenosine, cyclic 3',5'-(hydrogen phosphate) (CA INDEX NAME)

Absolute stereochemistry.



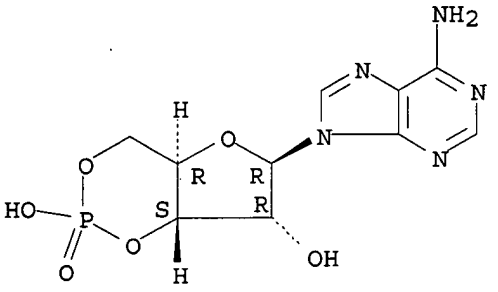
L9 ANSWER 23 OF 26 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1983:27586 CAPLUS
DOCUMENT NUMBER: 98:27586
ORIGINAL REFERENCE NO.: 98:4209a,4212a
TITLE: Interaction between amrinone and parathyroid hormone on bone in culture
AUTHOR(S): Krieger, Nancy S.; Stern, Paula H.
CORPORATE SOURCE: Med. Sch., Northwestern Univ., Chicago, IL, 60611, USA
SOURCE: American Journal of Physiology (1982), 243(6), E499-E504
CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB amrinone (I) [60719-84-8] inhibited release of Ca from neonatal mouse calvaria in organ culture stimulated by parathyroid hormone (PTH) [9002-64-6], 1,25-dihydroxyvitamin D3 [32222-06-3], or prostaglandin E2 [363-24-6]. Inhibition was dose-dependent and maximal at 2 + 10-4M. The effect of amrinone differed from the inhibitory effects of calcitonin, ouabain, or nigericin in that (1) 6-h exposure to amrinone alone prevented the effect of subsequently added PTH, (2) amrinone was only partially effective if added after resorption was initiated by 24-h treatment with PTH, (3) coincubation with amrinone and PTH during the first 48 h of culture allowed for a response to PTH after amrinone was removed; no such protection by a stimulator occurred with ouabain or nigericin. Also, submaximal concns. of amrinone plus calcitonin, ouabain, or nigericin gave greater than additive inhibition of Ca release. Amrinone had no effect on basal bone cAMP [60-92-4] or on the acute stimulation of cAMP by PTH. Apparently, amrinone could have a more direct interaction with the pathway involved in stimulated bone resorption than the other inhibitors.
IT 60-92-4
RL: BIOL (Biological study)
(amrinone interaction with parathyroid hormone in bone in relation to)
RN 60-92-4 CAPLUS
CN Adenosine, cyclic 3',5'-(hydrogen phosphate) (CA INDEX NAME)

Absolute stereochemistry.

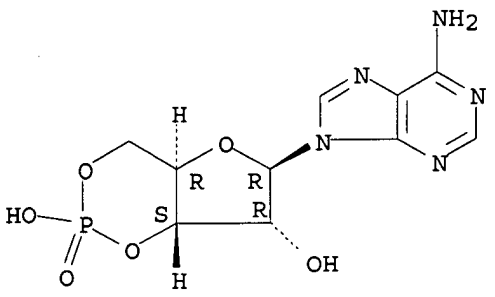


L9 ANSWER 24 OF 26 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1982:211384 CAPLUS
DOCUMENT NUMBER: 96:211384
ORIGINAL REFERENCE NO.: 96:34777a,34780a
TITLE: Parathyroid hormone and calcitonin interactions in bone: irradiation-induced inhibition of escape in vitro
AUTHOR(S): Krieger, Nancy S.; Feldman, Roy S.; Tashjian, Armen H., Jr.
CORPORATE SOURCE: Lab. Toxicol., Harvard Sch. Public Health, Boston, MA, 02115, USA
SOURCE: Calcified Tissue International (1982), 34(2), 197-203
CODEN: CTINDZ; ISSN: 0171-967X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Exposure of neonatal mouse calvaria in organ culture to γ-irradiation (6000 R) inhibited cell proliferation by 90% but had no effect on stimulation of bone resorption by parathyroid hormone (PTH) [9002-64-6]. However, the transient inhibition of hormone-stimulated bone resorption by calcitonin (escape) was decreased by irradiation, and the maximum response was observed at 6000 R. A dose of 6000 R did not affect the binding of 125I-labeled salmon calcitonin [47931-85-1] to calvaria and decreased PTH stimulation of cAMP [60-92-4] release from bone without affecting the cAMP response to human calcitonin [21215-62-3]. Although irradiation caused a dose-dependent inhibition of DNA synthesis, the dose-response curves for that effect and inhibition of escape were not superimposable. A morphol. study of hormonally treated calvaria demonstrated that irradiation prevented the early increase in number of osteoclasts in PTH-treated calvaria that had been observed previously in unirradiated bones. Autoradiog. showed that irradiation also prevented the PTH-stimulated recruitment of newly divided mononuclear cell precursors into osteoclasts. This may be correlated with the effect of irradiation to prevent the loss of responsiveness to calcitonin in the presence of PTH.

IT 60-92-4
RL: BIOL (Biological study)
(release of, by bone, parathyroid hormone and γ-rays effect on)
RN 60-92-4 CAPLUS
CN Adenosine, cyclic 3',5'-(hydrogen phosphate) (CA INDEX NAME)

Absolute stereochemistry.



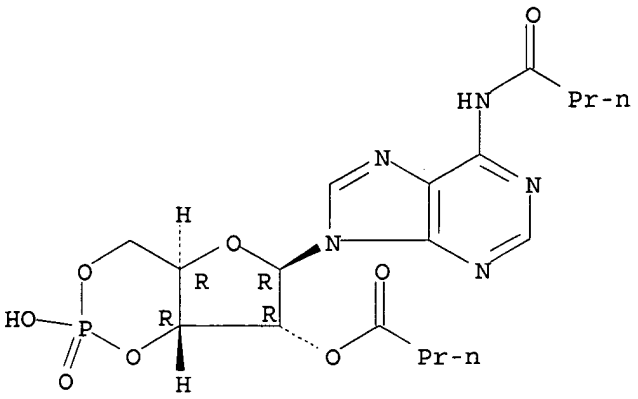
L9 ANSWER 25 OF 26 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1972:443522 CAPLUS
DOCUMENT NUMBER: 77:43522
ORIGINAL REFERENCE NO.: 77:7179a,7182a
TITLE: Effect of glucocorticoids on bone resorption in tissue culture
AUTHOR(S): Raisz, Lawrence G.; Trummel, Clarence L.; Wener, Jeffrey A.; Simmons, Hollis
CORPORATE SOURCE: Sch. Med. Dent., Univ. Rochester, Rochester, NY, USA
SOURCE: Endocrinology (1972), 90(4), 961-7
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cortisol (I) [50-23-7] at 10-6M inhibited the stimulation of bone resorption produced by vitamin A [68-26-8], prostaglandin E1 [745-65-3], and dibutyryl cyclic 3',5'-adenosine monophosphate [362-74-3] in continuous culture but was less effective in inhibiting the response to parathyroid hormone [9002-64-6] or 25-hydroxycholecalciferol [19356-17-3]. However, in induction expts. when I (10-5-10-6M) was given before and during a brief application of parathyroid hormone or 25-hydroxycholecalciferol, the subsequent resorptive response was blocked. This effect was specific for steroids with glucocorticoid activity. When I at 10-6-10-8M was added after induction by parathyroid hormone or 25-hydroxycholecalciferol, it was ineffective in inhibiting resorption by itself but could enhance the inhibitory effects of salmon calcitonin (SCT) [47931-85-1]. SCT alone produced a transient inhibition of resorption in bones previously induced with parathyroid hormone, followed by escape. When I and SCT were given together the inhibition of resorption was greater than with SCT alone and escape was prevented.

IT 362-74-3
RL: BIOL (Biological study)
(bone resorption stimulation by, cortisol inhibition of)

RN 362-74-3 CAPLUS
CN Adenosine, N-(1-oxobutyl)-, cyclic 3',5'-(hydrogen phosphate) 2'-butanoate (CA INDEX NAME)

Absolute stereochemistry.



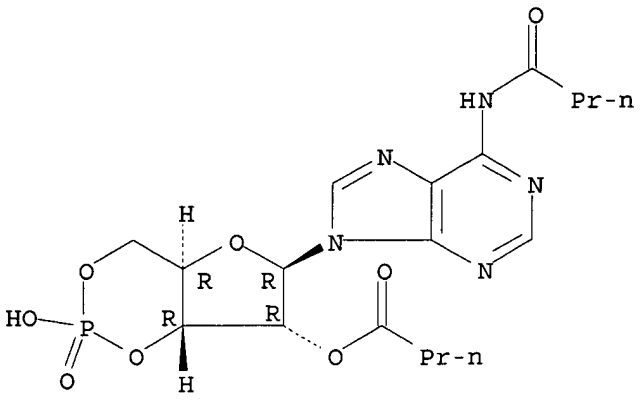
L9 ANSWER 26 OF 26 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1972:443504 CAPLUS
DOCUMENT NUMBER: 77:43504
ORIGINAL REFERENCE NO.: 77:7175a,7178a
TITLE: Escape from inhibition of resorption in cultures of fetal bone treated with calcitonin and parathyroid hormone
AUTHOR(S): Wener, Jeffrey A.; Gorton, Steven J.; Raisz, Lawrence G.
CORPORATE SOURCE: Sch. Med. Dent., Univ. Rochester, Rochester, NY, USA
SOURCE: Endocrinology (1972), 90(3), 752-9
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Initially calcitonin (CT) [9007-12-9] completely inhibited the increase in bone resorption produced by bovine parathyroid hormone (PTH) or 25-hydroxycholecalciferol (HCC) [19356-17-3] in fetal rat long bone shafts in tissue culture, but this effect was transient. After a period of inhibition varying from less than 36 hr to several days, there was escape, i.e., resorption began to increase despite fresh CT addns. This occurred with salmon, human, or rat CTs. Escape did not occur when spontaneous resorption in control, untreated bones was blocked by CT, or when CT inhibited resorption produced by vitamin A [11103-57-4], prostaglandin E1 [745-65-3], or dibutyryl-cyclic AMP [362-74-3]. Escape was observed with calvaria as well as long bones stimulated with PTH. Escape also occurred in the absence of PTH or HCC when the bones were pretreated with maximal doses of the above stimulators to induce resorption, and then treated with CT. Escape was prevented or delayed by decreasing the concns. of calcium [7440-70-2] or phosphate [14265-44-2] in the medium.

IT 362-74-3
RL: BIOL (Biological study)
(bone resorption from, calcitonin inhibition of)

RN 362-74-3 CAPLUS
CN Adenosine, N-(1-oxobutyl)-, cyclic 3',5'-(hydrogen phosphate) 2'-butanoate (CA INDEX NAME)

Absolute stereochemistry.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FORMAT

L9 ANSWER 7 OF 26 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2006:605344 CAPLUS
DOCUMENT NUMBER: 145:40309
TITLE: Agent for regulating bone formation
INVENTOR(S): Shimizu, Hideo; Nakagami, Hironori; Morishita, Ryuichi
PATENT ASSIGNEE(S): Anges Mg, Inc., Japan
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006064886	A1	20060622	WO 2005-JP23078	20051215
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CA 2591715	A1	20060622	CA 2005-2591715	20051215
EP 1839664	A1	20071003	EP 2005-816428	20051215
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PRIORITY APPLN. INFO.:

JP 2004-365148	A	20041216
JP 2005-234311	A	20050812
WO 2005-JP23078	W	20051215

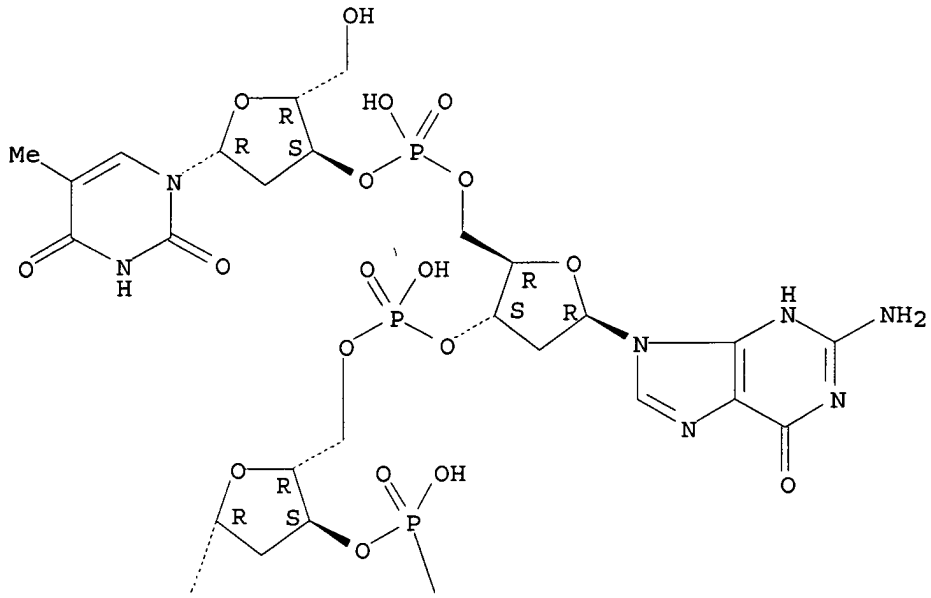
AB It is intended to provide a preventive, ameliorating and/or therapeutic agent for a disease caused by the rupture of equilibrium in bone formation and bone resorption. A decoy of the invention induces normal bone metabolism by inhibiting a differentiation-inducing factor for a cell associated with bone metabolism For example, by inhibiting NF-κB, which is a transcriptional regulatory factor that regulates the differentiation of an osteoclast, bone resorption can be controlled. Because the method utilizes a mechanism that is different from that of a conventional agent, an effect can be expected in a case where a conventional agent has not exerted any effect. For example, a NF-κB decoy 5'-CCTTGAAGGGATTTCCCTCC-3' inhibited vitamin D3-induced induction of osteoclast in vitro.

IT 118904-07-7
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(AP-1 decoy sequence; agents for regulating bone formation containing bone-forming transcription factor-binding nucleic acids)

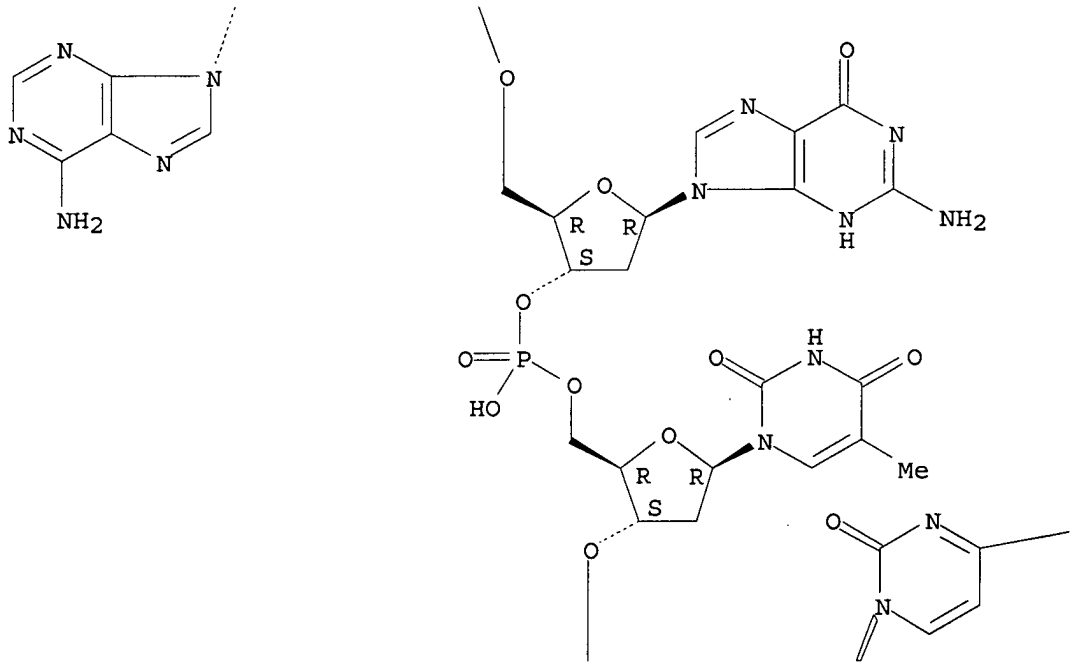
RN 118904-07-7 CAPLUS
CN Adenosine, thymidylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxyadenylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-thymidylyl-(3'→5')-2'-deoxycitydylyl-(3'→5')-2'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.

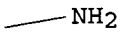
PAGE 1-A



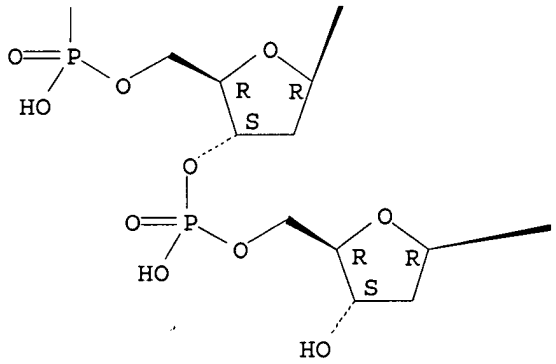
PAGE 2-A



PAGE 2-B



PAGE 3-A



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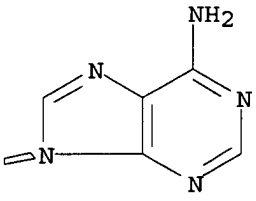
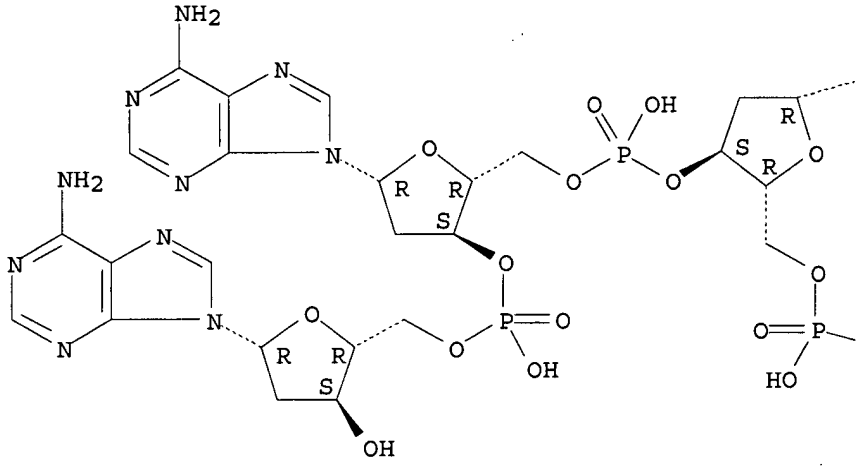


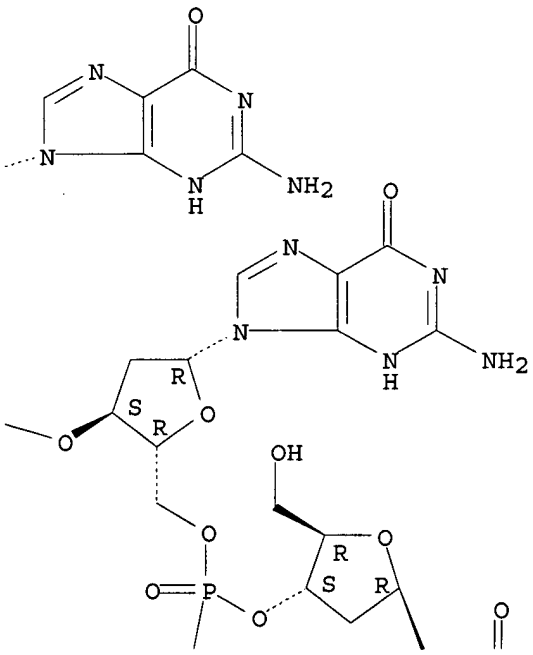
IT 288066-83-1
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Ets decoy sequence; agents for regulating bone formation containing bone-forming transcription factor-binding nucleic acids)
RN 288066-83-1 CAPLUS
CN Adenosine, 2'-deoxycytidylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxyadenylyl-(3'→5')-2'-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

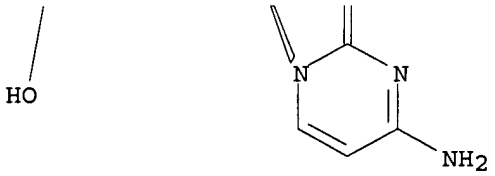
PAGE 1-A



PAGE 1-B



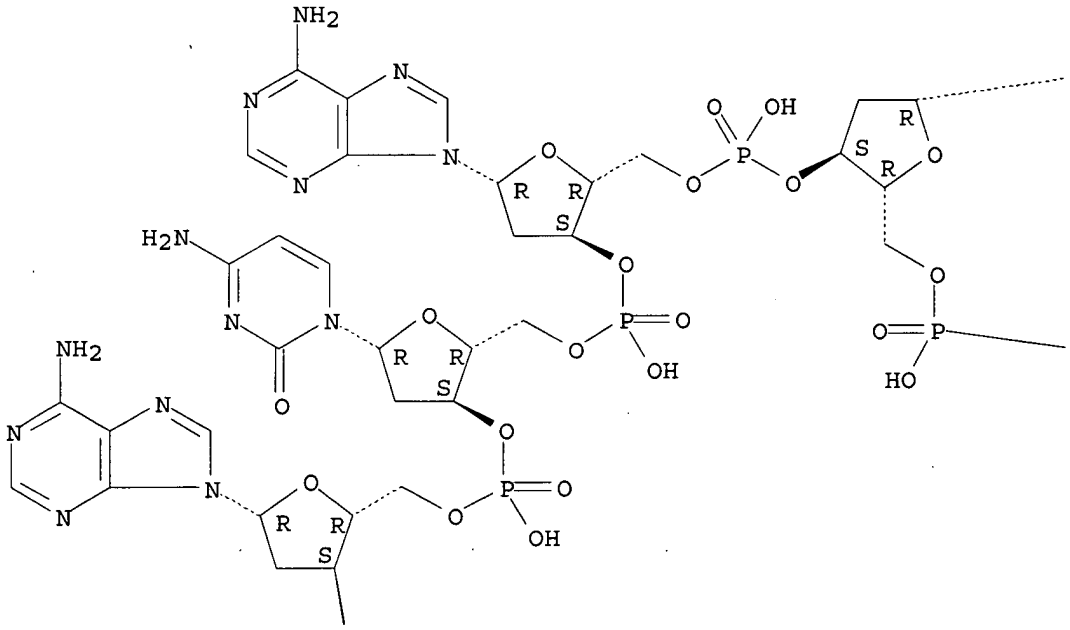
PAGE 2-B



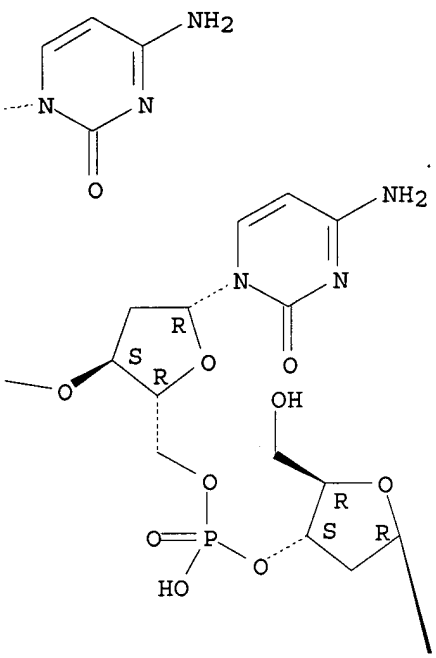
IT 184875-67-0 216530-24-4
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Runx2/Cbfa1 decoy sequence; agents for regulating bone formation containing bone-forming transcription factor-binding nucleic acids)
RN 184875-67-0 CAPLUS
CN Adenosine, 2'-deoxyadenylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxyadenylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

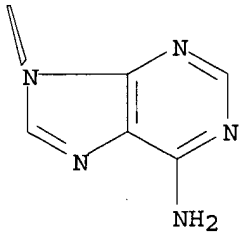


PAGE 1-B



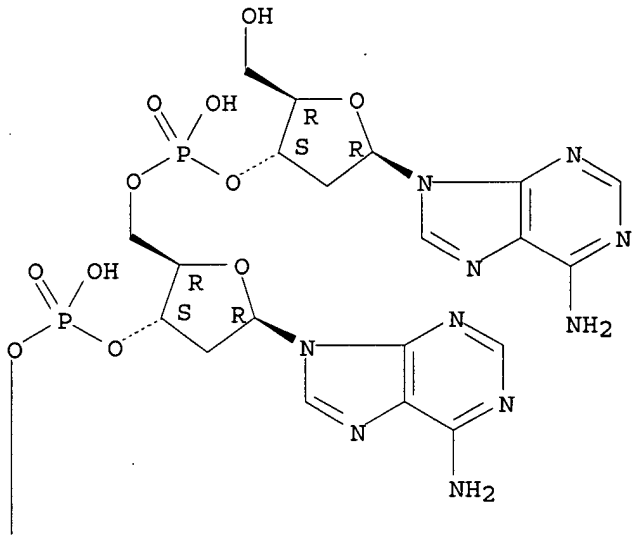
PAGE 2-A

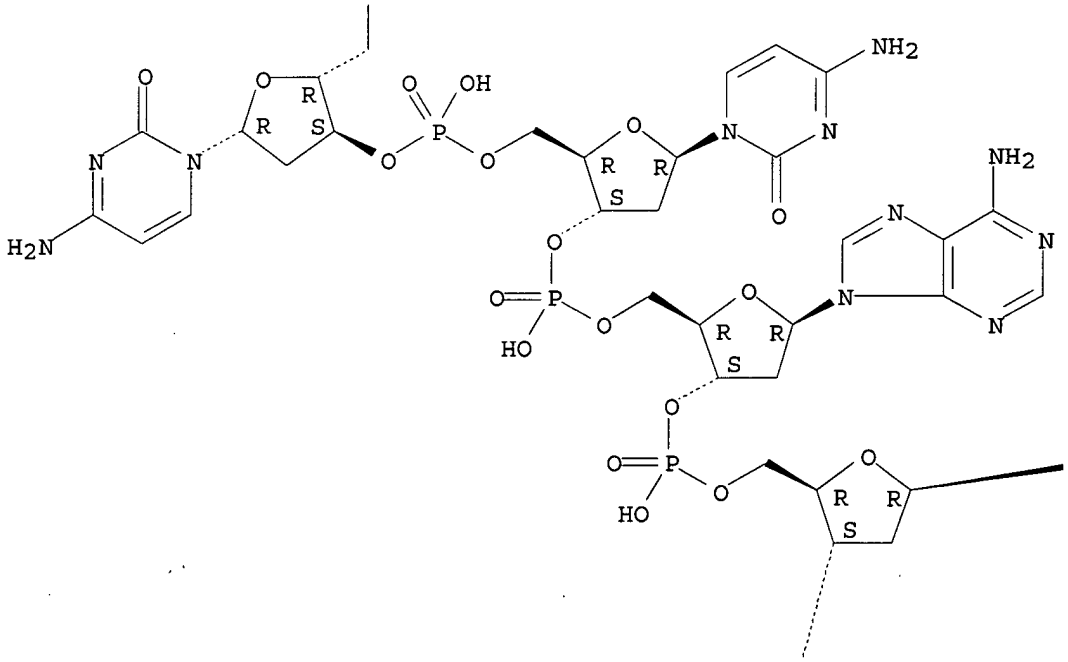
PAGE 2-B



RN 216530-24-4 CAPLUS
CN Adenosine, 2'-deoxyadenylyl-(3'→5')-2'-deoxyadenylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxyadenylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.





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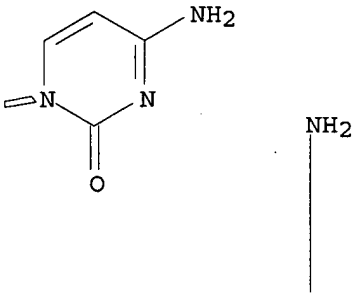

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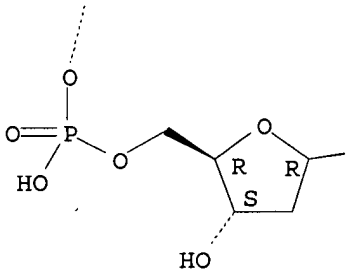

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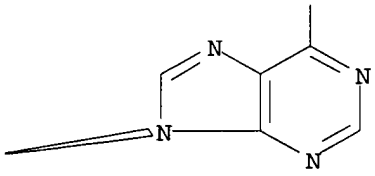


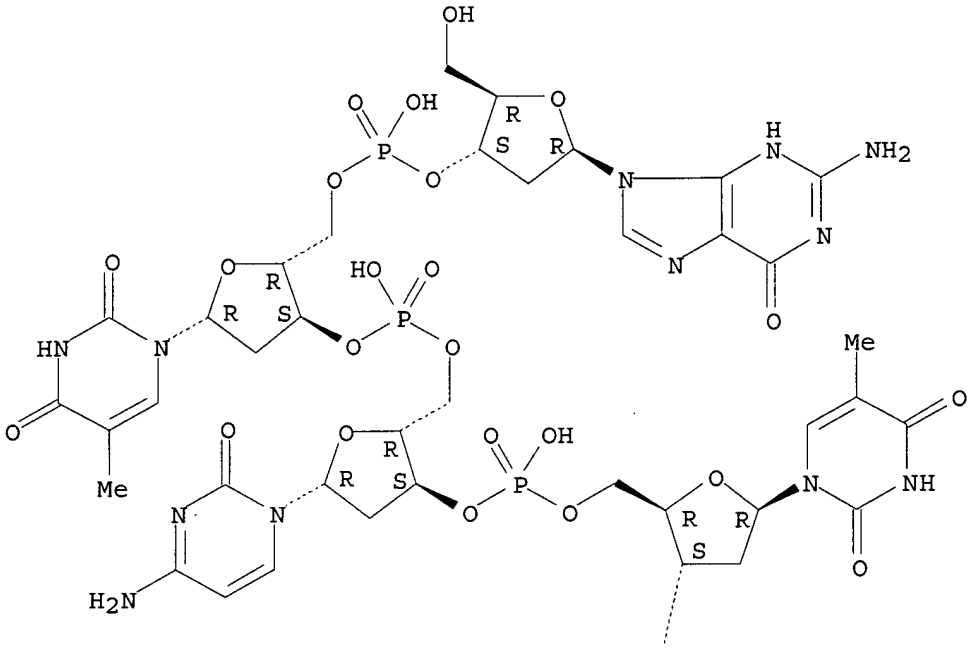
IT 104040-02-0 240482-84-2 487016-74-0
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Smad decoy sequence; agents for regulating bone formation containing bone-forming transcription factor-binding nucleic acids)

RN 104040-02-0 CAPLUS

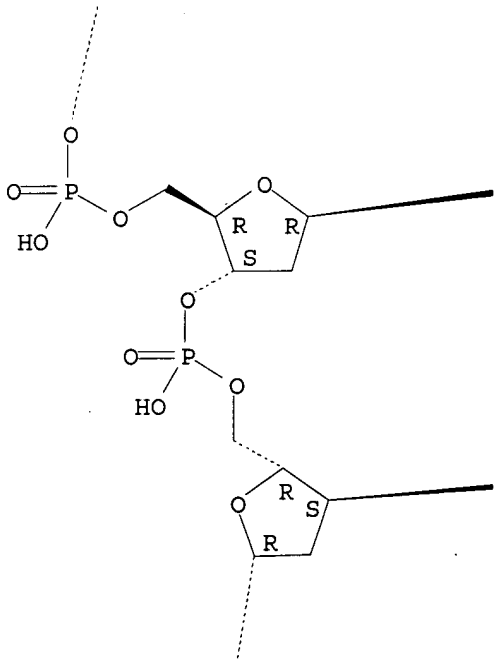
CN Cytidine, 2'-deoxyguanylyl-(3'→5')-thymidylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-thymidylyl-(3'→5')-2'-deoxyadenylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxyadenylyl-(3'→5')-2'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.

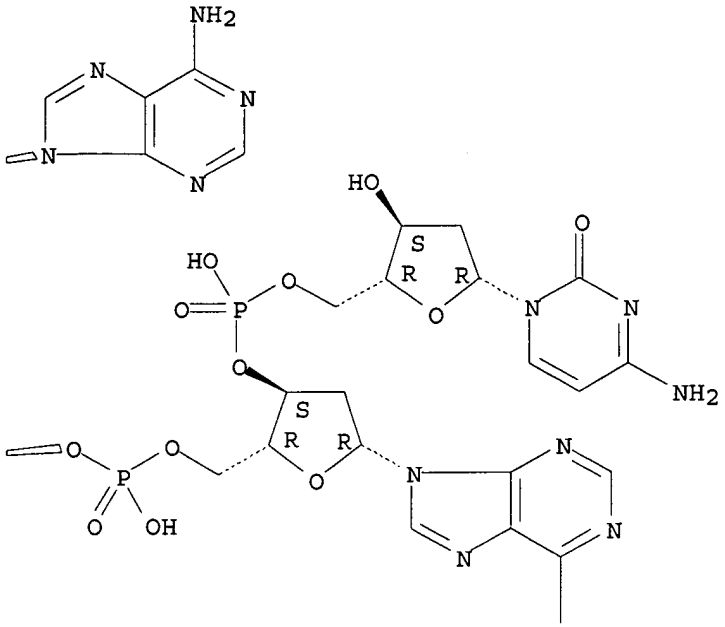
PAGE 1-A



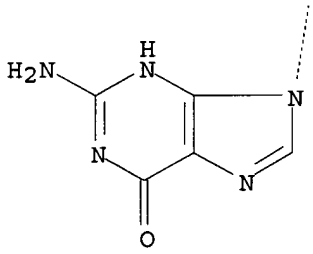
PAGE 2-A



PAGE 2-B



PAGE 3-A

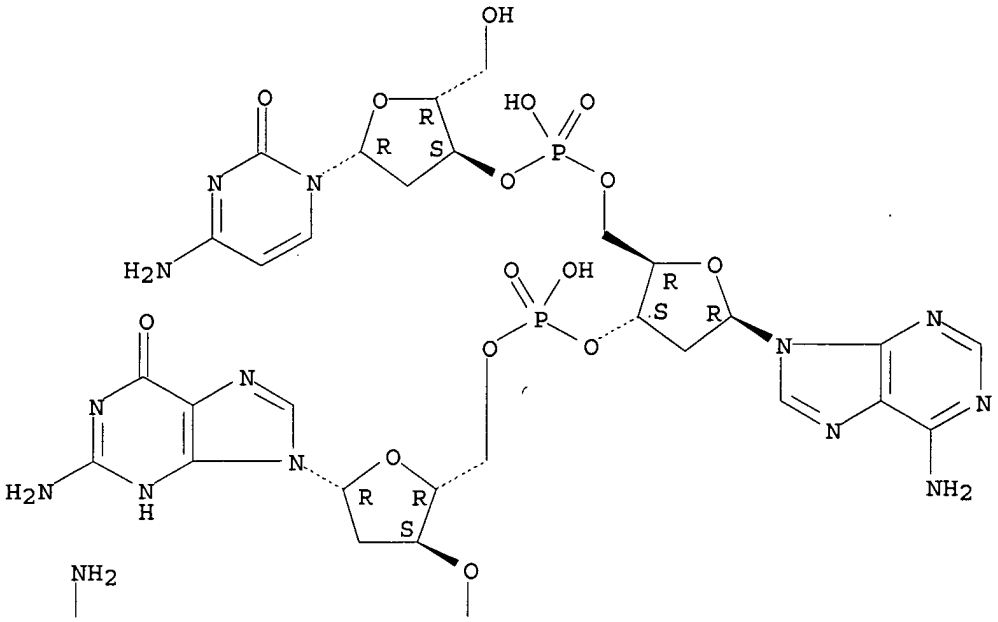


PAGE 3-B

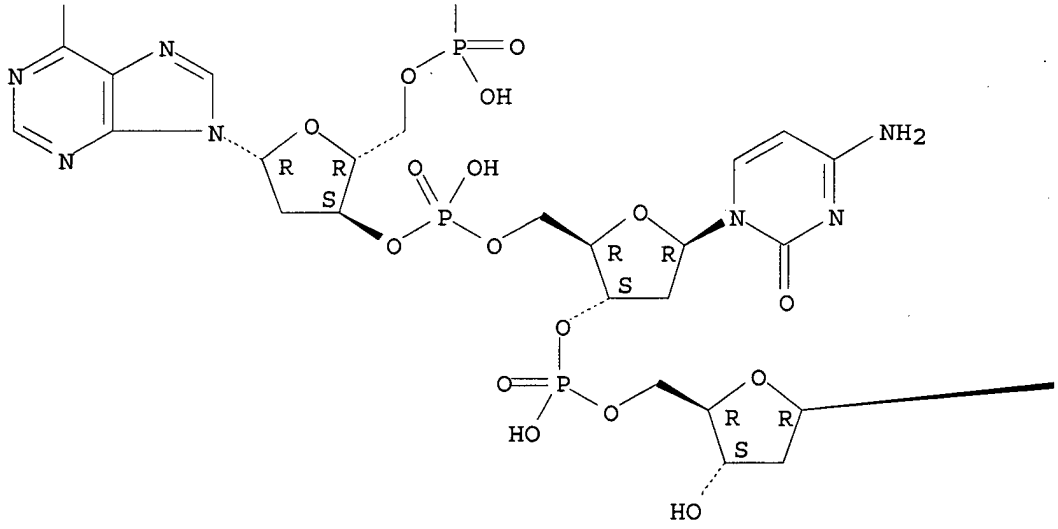
RN 240482-84-2 CAPLUS
CN Adenosine, 2'-deoxycytidylyl-(3'→5')-2'-deoxyadenylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxyadenylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxy- (9CI) (CA INDEX NAME)

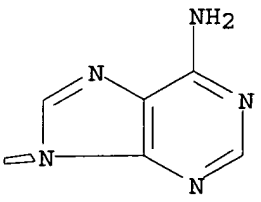
Absolute stereochemistry.

PAGE 1-A



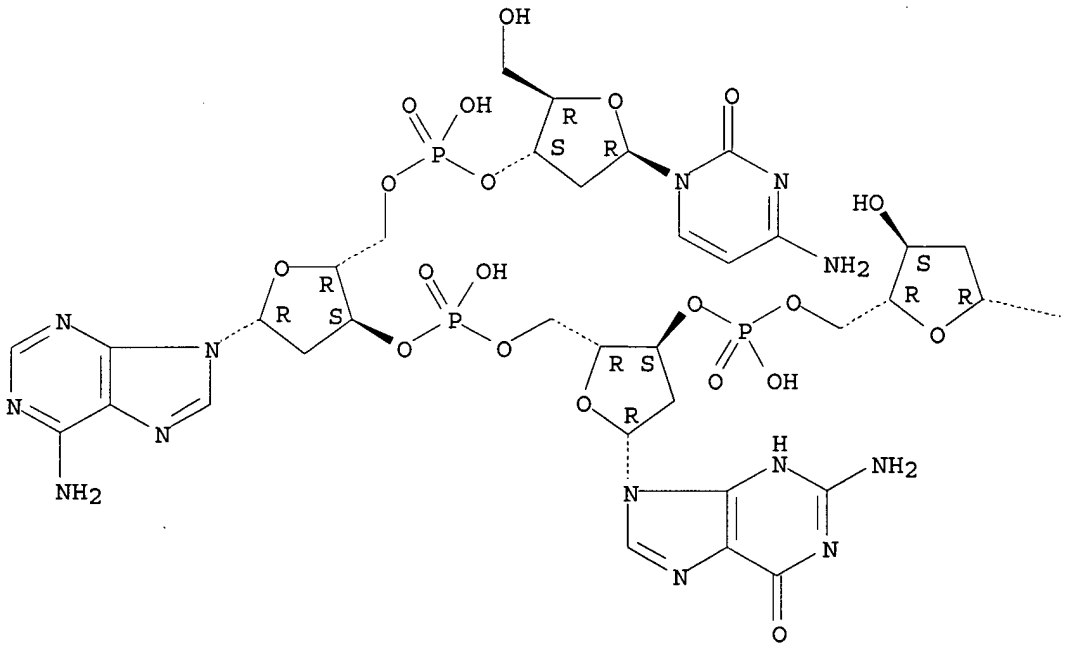
PAGE 2-A

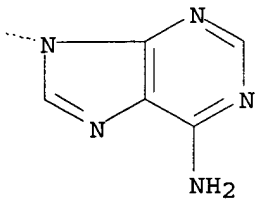




RN 487016-74-0 CAPLUS
CN Adenosine, 2'-deoxycytidylyl-(3'→5')-2'-deoxyadenylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.





REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

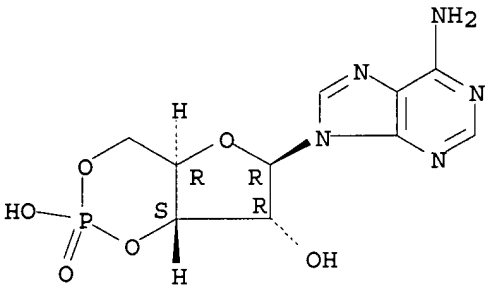
L9 ANSWER 8 OF 26 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2006:389961 CAPLUS
DOCUMENT NUMBER: 145:59994
TITLE: cAMP-PKA signaling pathway regulates bone resorption mediated by processing of cathepsin K in cultured mouse osteoclasts
AUTHOR(S): Park, Young-Guk; Kim, Young-Hun; Kang, Sung-Koo; Kim, Cheorl-Ho
CORPORATE SOURCE: Department of Orthodondritics, Kyung-Hee University College of Dental Medicine, Seoul, 130-701, S. Korea
SOURCE: International Immunopharmacology (2006), 6(6), 947-956
CODEN: IINMBA; ISSN: 1567-5769
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cathepsin K (Cat K) is the major cysteine protease expressed in osteoclast and is thought to play a key role in matrix degradation during bone resorption. It is shown that the intracellular maturation of Cat K was prevented by the cAMP antagonist, Rp-cAMP, and the protein kinase A (PKA) inhibitors of KT5720 and H89. In contrast, forskolin, an adenylate cyclase agonist, rather induced Cat K processing and maturation in osteoclast. Furthermore, to determine whether Cat K processing and maturation signaling involves protein kinase C (PKC), mouse total bone cells were treated with calphostin C, a specific inhibitor of PKC, however, no effect was observed, indicating that PKC calphostin C did not affect to osteoclast-mediated Cat K processing and maturation in osteoclast. Thus, it is indicated that the cAMP-PKA signaling pathway regulate Cat K maturation in osteoclast. Since secreted proenzymes have the potential to reenter the cell via M6P receptor, to prevent this possibility, we tested cAMP antagonist Rp-cAMP and the PKA inhibitors KT5720 and H89 in the absence or presence of M6P. Inhibition of Cat K processing by Rp-cAMP, KT5720 or H89 was observed in a dose-dependent manner. Furthermore, the addition of M6P resulted in enhanced potency of Rp-cAMP, KT5720 and H89, which dose-dependently inhibited in vitro bone resorption with potency similar to that observed for inhibition of Cat K processing.

IT 60-92-4, CAMP
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cAMP-PKA signaling regulated bone resorption mediated by processing of cathepsin K in mouse osteoclasts)

RN 60-92-4 CAPLUS
CN Adenosine, cyclic 3',5'-(hydrogen phosphate) (CA INDEX NAME)

Absolute stereochemistry.

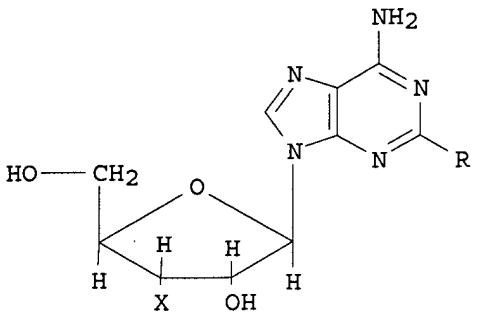


REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 9 OF 26 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:754440 CAPLUS
DOCUMENT NUMBER: 141:271600
TITLE: Use of adenosine receptor agonists in therapy
INVENTOR(S): Richardson, Peter
PATENT ASSIGNEE(S): Cambridge Biotechnology Ltd., UK
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004078184	A1	20040916	WO 2004-GB952	20040305
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004216891	A1	20040916	AU 2004-216891	20040305
CA 2514848	A1	20040916	CA 2004-2514848	20040305
EP 1603576	A1	20051214	EP 2004-717693	20040305
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK				
CN 1809365	A	20060726	CN 2004-80005723	20040305
JP 2006519824	T	20060831	JP 2006-505924	20040305
NO 2005004475	A	20050927	NO 2005-4475	20050927
IN 2005CN02547	A	20070831	IN 2005-CN2547	20051005
US 2006234975	A1	20061019	US 2006-547454	20060628
PRIORITY APPLN. INFO.:			GB 2003-5150 A	20030307
			WO 2004-GB952 W	20040305

OTHER SOURCE(S): MARPAT 141:271600
GI



I

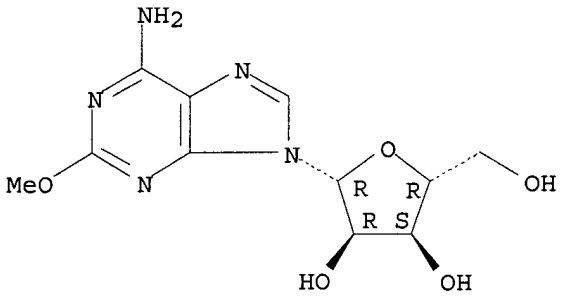
AB The invention describes the use of compds. I (R = C1-4 alkoxy; X = H, OH) for the prevention, treatment, or amelioration of cancer, inflammation, autoimmune disease, ischemia-reperfusion injury, epilepsy, sepsis, septic shock, neurodegeneration (including Alzheimer's Disease), muscle fatigue or muscle cramp. The compds. are effective at very low doses, and so can be administered at doses at which serious side effects are not observed

IT 24723-77-1, 2-Methoxyadenosine
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(adenosine receptor agonists for therapy)

RN 24723-77-1 CAPLUS

CN Adenosine, 2-methoxy- (CA INDEX NAME)

Absolute stereochemistry.

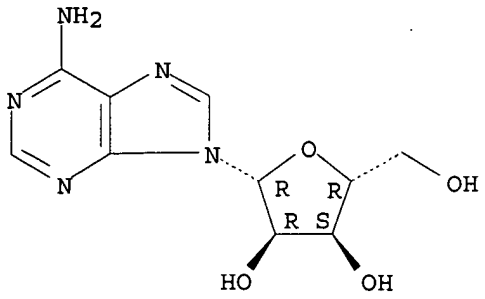


IT 58-61-7D, Adenosine, derivs. 73-03-0D, 3'-Deoxyadenosine, derivs. 50257-84-6 50447-10-4, 2-Ethoxyadenosine 756819-11-1 756819-12-2 756819-13-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(adenosine receptor agonists for therapy)

RN 58-61-7 CAPLUS

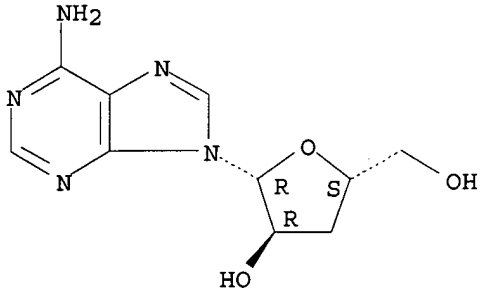
CN Adenosine (CA INDEX NAME)

Absolute stereochemistry.



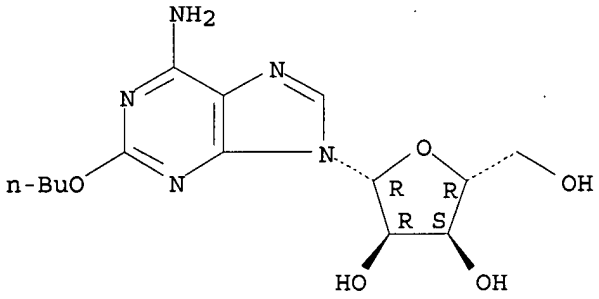
RN 73-03-0 CAPLUS
CN Adenosine, 3'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.



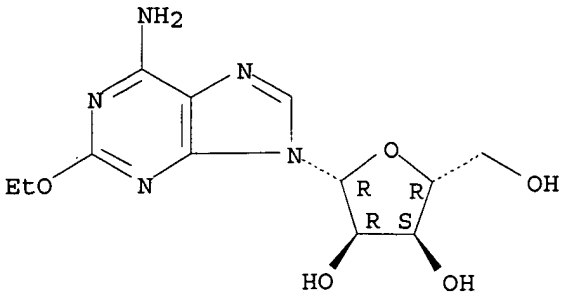
RN 50257-84-6 CAPLUS
CN Adenosine, 2-butoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



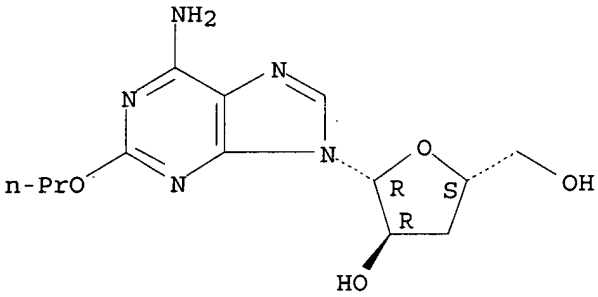
RN 50447-10-4 CAPLUS
CN Adenosine, 2-ethoxy- (CA INDEX NAME)

Absolute stereochemistry.



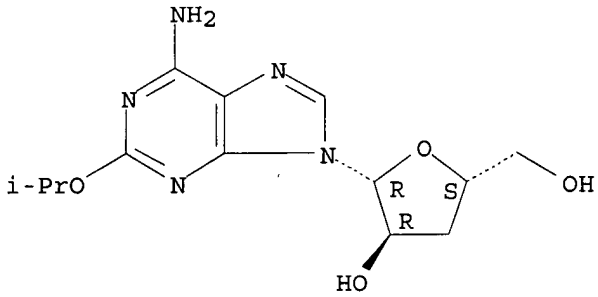
RN 756819-11-1 CAPLUS
CN Adenosine, 3'-deoxy-2-propoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



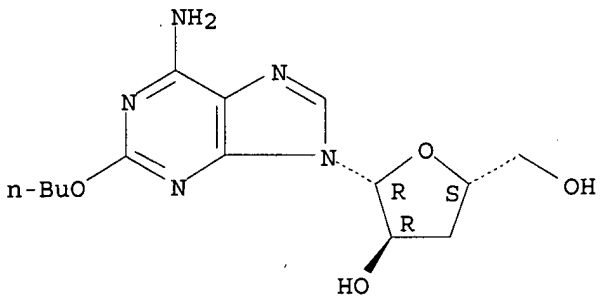
RN 756819-12-2 CAPLUS
CN Adenosine, 3'-deoxy-2-(1-methylethoxy)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 756819-13-3 CAPLUS
CN Adenosine, 2-butoxy-3'-deoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



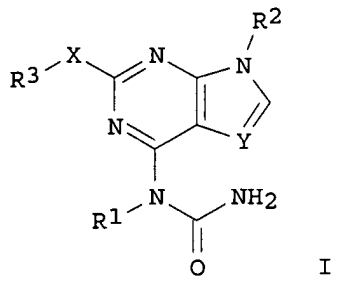
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 10 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:421319 CAPLUS
DOCUMENT NUMBER: 141:116242
TITLE: Novel bone-targeted Src tyrosine kinase inhibitor drug discovery. [Erratum to document cited in CA140:191893]
AUTHOR(S): Shakespeare, William C.; Metcalf, Chester A., III; Wang, Yihan; Sundaramoorthi, Raji; Keenan, Terence; Weigele, Manfred; Bohacek, Regine S.; Dalgarno, David C.; Sawyer, Tomi K.
CORPORATE SOURCE: ARIAD Pharmaceuticals Inc., Cambridge, MA, 02139-4234, USA
SOURCE: Current Opinion in Drug Discovery & Development (2003), 6(6), 978
CODEN: CODDFF; ISSN: 1367-6733
PUBLISHER: Current Drugs
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The corrected structure 7 in Figure 4 is given.

L12 ANSWER 11 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:220147 CAPLUS
DOCUMENT NUMBER: 140:270865
TITLE: Preparation of substituted pyrrolo[2,3-d]pyrimidin-4-yl compounds as inhibitors of CSBP/p38 kinase
INVENTOR(S): Adams, Jerry Leroy; Boehm, Jeffrey C.; Wan, Zehong
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004021979	A2	20040318	WO 2003-US26508		20030826
WO 2004021979	A3	20040930			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
AU 2003265636	A1	20040329	AU 2003-265636		20030826
EP 1551410	A2	20050713	EP 2003-794501		20030826
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
JP 2006503826	T	20060202	JP 2004-534320		20030826
US 2005288503	A1	20051229	US 2005-525478		20050224
PRIORITY APPLN. INFO.:			US 2002-408832P	P	20020906
			WO 2003-US26508	W	20030826

OTHER SOURCE(S): MARPAT 140:270865
GI



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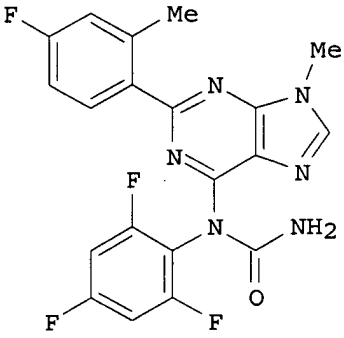


II

AB Title compds. I [X = bond, O, N, or S; Y = C or N; R1 = H, (un)substituted alkyl, cycloalkyl, cycloalkylalkyl, aryl, etc.; R2 = (un)substituted alkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, etc.; R3 = (un)substituted aryl or heteroaryl] and their pharmaceutically acceptable salts are prepared and disclosed as CSBP/p38 kinase inhibitors. Thus, e.g., II, was prepared via reaction of [2-(4-fluoro-2-methylphenyl)-9-methyl-9H-purin-6-yl]-(2,4,6-trifluorophenyl)amine (preparation given) with triphosgene and ammonia . In CSBP/p38 kinase assays, representative compds. of the invention showed pos. inhibitory activity at <50 μM. Compns. of I for use in therapy are also claimed.

L12 ANSWER 12 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:203835 CAPLUS
DOCUMENT NUMBER: 140:235754
TITLE: Preparation of heteroaryl nitriles for treating disorders involving cathepsin K
INVENTOR(S): Altmann, Eva; Betschart, Claudia; Hayakawa, Kenji; Irie, Osamu; Sakaki, Junichi; Iwasaki, Genji; Lattmann, Rene; Missbach, Martin; Teno, Naoki
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis Pharma G.m.b.H.
SOURCE: PCT Int. Appl., 110 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004020441	A1	20040311	WO 2003-EP9621	20030829

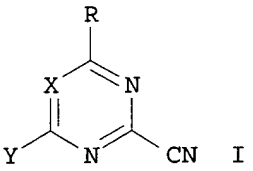
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SY, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW
RW: AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE,

DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR

CA 2494931	A1	20040311	CA 2003-2494931	20030829
AU 2003266330	A1	20040319	AU 2003-266330	20030829
EP 1537111	A1	20050608	EP 2003-790945	20030829
EP 1537111	B1	20070502		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003013968	A	20050719	BR 2003-13968	20030829
CN 1678613	A	20051005	CN 2003-820604	20030829
JP 2006500385	T	20060105	JP 2004-532149	20030829
AT 361300	T	20070515	AT 2003-790945	20030829
ES 2285239	T3	20071116	ES 2003-3790945	20030829
US 2006142575	A1	20060629	US 2005-525658	20050823
PRIORITY APPLN. INFO.:			GB 2002-20187 A	20020830
			WO 2003-EP9621 W	20030829

OTHER SOURCE(S): MARPAT 140:235754

GI



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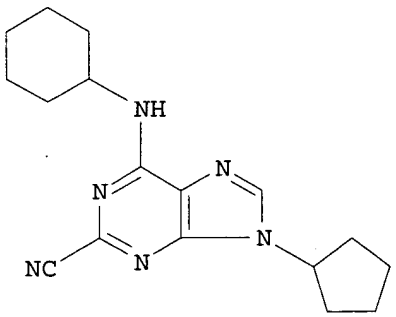


II

AB The invention provides heteroaryl nitriles (shown as I; variables defined below; the examples are mostly pyrimidines, quinazolines and purines, e.g. II) or a pharmaceutically acceptable salt or ester thereof, which are inhibitors of cathepsin K and find use pharmaceutically for treatment of diseases and medical conditions in which cathepsin K is implicated, e.g. various disorders including inflammation, rheumatoid arthritis, osteoarthritis, osteoporosis and tumors. Compds. I typically have Ki's for human cathepsin K of .ltorsim.50 nM, preferably of .ltorsim.5 nM, e.g. .apprx.1 nM; values for individual I are not given. For I: R is H, -R2, -OR2 or NR1R2, wherein R1 is H, lower alkyl or C3-C10 cycloalkyl, and R2 is lower alkyl or C3-C10 cycloalkyl, and wherein R1 and R2 are (un)substituted by halo, hydroxy, lower alkoxy, CN, NO2, or optionally mono- or di-lower alkyl substituted amino; X is :N- or :C(Z)-, wherein Z is H, -R4, -C.tplbond.C-CH2-R5, C(P):C(Q)-R3; Y = -NR8R9; Z and Y together with the C atoms to which they are attached can be joined to provide a ring; addnl. details are given in the claims. Methods of preparation are claimed and many example prepns. are included. For example, II was prepared in 3 steps starting with N-heteroarylation of cyclohexylamine by 2,6-dichloropurine followed by N-cycloalkylation of the purine by bromocyclopentane, followed by substitution of Cl in 2-chloro-6-cyclohexylamino-9-cyclopentylpurine by NaCN.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 13 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:817435 CAPLUS

DOCUMENT NUMBER: 140:191893

TITLE: Novel bone-targeted Src tyrosine kinase inhibitor drug discovery

AUTHOR(S): Shakespeare, William C.; Metcalf, Chester A., III;

Wang, Yihan; Sundaramoorthi, Raji; Keenan, Terence; Weigele, Manfred; Bohacek, Regine S.; Dalgarno, David C.; Sawyer, Tomi K.

CORPORATE SOURCE: ARIAD Pharmaceuticals Inc, Cambridge, MA, 02139-4234, USA

SOURCE: Current Opinion in Drug Discovery & Development (2003), 6(5), 729-741
CODEN: CODDFF; ISSN: 1367-6733

PUBLISHER: Current Drugs

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Bone-targeted Src tyrosine kinase (STK) inhibitors have recently been developed for the treatment of osteoporosis and cancer-related bone diseases. The concept of bone targeting derives from bisphosphonates, and from the evolution of such mols. in terms of therapeutic efficacy for the treatment of bone disorders. Interestingly, some of the earliest bisphosphonates were recognized for their ability to inhibit calcium carbonate precipitation (scaling) by virtue of their affinity to chelate calcium. This chelating property was subsequently exploited in the development of bisphosphonate analogs as inhibitors of the bone-resorbing cells known as osteoclasts, giving rise to breakthrough medicines, such as Fosamax (for the treatment of osteoporosis) and Zometa (for the treatment of osteoporosis and bone metastases). Relative to these milestone achievements, there is a tremendous opportunity to explore beyond the limited chemical space (functional group diversity) of such bisphosphonates to design novel bone-targeting moieties, which may be used to develop other classes of promising small-mol. drugs affecting different biol. pathways. Here, the authors review studies focused on bone-targeted inhibitors of STK, a key enzyme in osteoclast-dependent bone resorption. Two strategies are described relative to bone-targeted STK inhibitor drug discovery: (i) the development of novel Src homol. (SH)-2 inhibitors incorporating non-hydrolyzable phosphotyrosine mimics and exhibiting mol. recognition and bone-targeting properties, leading to the in vivo-effective lead compound AP-22408; and (ii) the development of novel ATP-based Src kinase inhibitors incorporating bone-targeting moieties, leading to the in vivo-effective lead compound AP-23236. In summary, AP-22408 and AP-23236, which differ mechanistically by virtue of blocking Src-dependent non-catalytic or catalytic activities in osteoclasts, exemplify ARIAD Pharmaceuticals' structure-based design of novel bone-targeted lead compds., successfully achieving in vivo proof-of-concept and providing the framework for the next-generation mols. that have further advanced, in terms of preclin. studies, for the treatment of osteoporosis and related bone diseases, including osteolytic bone metastases.

REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2002:801211 CAPLUS

DOCUMENT NUMBER: 139:78459

TITLE: Tenofovir treatment at 30 mg/kg/day can inhibit cortical bone mineralization in growing rhesus monkeys (Macaca mulatta)

AUTHOR(S): Castillo, Alesha B.; Tarantal, Alice F.; Watnik, Mitchell R.; Bruce Martin, R.

CORPORATE SOURCE: School of Medicine, Orthopaedic Research Laboratories, University of California at Davis Medical Center, Sacramento, CA, 95817, USA

SOURCE: Journal of Orthopaedic Research (2002), 20(6), 1185-1189
CODEN: JOREDR; ISSN: 0736-0266

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The acyclic nucleoside phosphonate analog, 9-[2-(R)-(phosphonomethoxy)propyl]adenine (PMPA; Tenofovir; Gilead Sciences, Inc., Foster City, CA), has been shown to effectively inhibit simian immunodeficiency virus (SIV) replication in rhesus macaques by blocking reverse transcription. However, chronic long-term tenofovir treatment at 30 mg/kg/day, intended to reduce viral replication and illness, has been shown to result in bone deformities and spontaneous fractures in rhesus monkeys. Based on these findings, we studied the effects of tenofovir treatment and pathogenic SIV infection on cortical bone remodeling in rhesus monkeys. Tibiae from tenofovir-treated or untreated, SIV-infected or uninfected, rhesus macaques were evaluated for bone microdamage and remodeling. We found that tenofovir treatment had a significant effect on osteoid (unmineralized bone) seam width in tibial cross-sections. Regardless of SIV infection status, half of the tenofovir-treated animals had significantly increased osteoid seam widths in tibial cortical bone resulting in an osteomalacia-like condition. Pathogenic SIV infection significantly increased tibial resorption cavity d., and this increase was normalized by tenofovir treatment. These results suggest that tenofovir treatment at 30 mg/kg/day inhibits mineralization of newly formed bone. SIV infection results in increased tibial resorption cavity d., while tenofovir treatment tends to minimize this increase. Both defective mineralization of newly formed bone and increased resorption cavity d. may result in greater bone fragility.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2002:429543 CAPLUS

DOCUMENT NUMBER: 137:6038

TITLE: Preparation of purine derivatives as bone resorption inhibitors

INVENTOR(S): Weigele, Manfred; Sawyer, Tomi K.; Bohacek, Regine; Shakespeare, William C.; Sundaramoorthi, Rajeswari; Wang, Yihan; Dalgarno, David C.; Metcalf, Chester A.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 99 pp., Cont.-in-part of U.S. Ser. No. 740,267.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

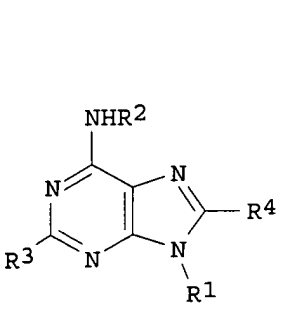
FAMILY ACC. NUM. COUNT: 5

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2002068721	A1	20020606	US 2000-740393		20001218
US 7115589	B2	20061003			
US 2002103161	A1	20020801	US 2000-740267		20001218
US 2002132819	A1	20020919	US 2000-740653		20001218
AT 327242	T	20060615	AT 2000-986551		20001218
US 2005096298	A1	20050505	US 2004-994962		20041122
PRIORITY APPLN. INFO.:			US 1999-172161P	P	19991217
			US 1999-172510P	P	19991217
			US 2000-240788P	P	20001016
			US 2000-740267	A2	20001218
			US 2000-740653	A2	20001218
			US 2000-740619	A	20001218

OTHER SOURCE(S): MARPAT 137:6038

GI



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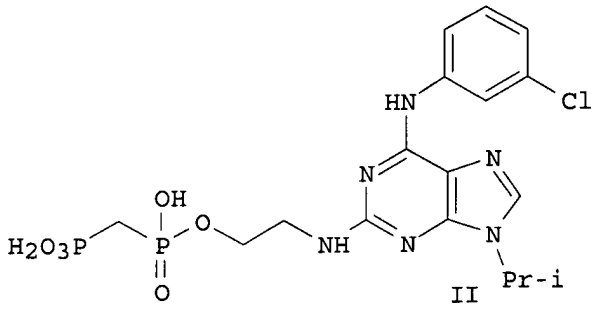

II

AB Purine derivs. of formula I [R1 = H, aliphatic, heteroaliph., aryl, or heteroaryl moiety; R2 = aliphatic, heteroaliph., aryl, or heteroaryl moiety; R3, R4 = H, halo, (substituted) OH, (substituted) NH, (substituted) SH, aliphatic, heteroaliph., aryl, or heteroaryl moiety] are prepared for use as bone resorption inhibitors. Thus, II was prepared from 2-amino-6-chloropurine, 2-propanol, 3-chloroaniline, ethanolamine and methylenebis(phosphonic dichloride). The preferred compds. I have IC50 values below 500 nM in the anti-resorption cell assay on white rabbits.

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:87195 CAPLUS
DOCUMENT NUMBER: 136:134796
TITLE: Preparation of acyl guanidino derivatives as inhibitors of cell adhesion
INVENTOR(S): Peyman, Anuschirwan; Will, David; Gadek, Thomas R.; Knolle, Jochen; McDowell, Robert; Gourvest, Jean-Francois; Ruxer, Jean-Marie
PATENT ASSIGNEE(S): Aventis Pharma Deutschland G.m.b.H., Germany; Genentech, Inc.
SOURCE: Eur. Pat. Appl., 34 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1176145	A1	20020130	EP 2000-116385	20000728
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
WO 2002010168	A1	20020207	WO 2001-EP8485	20010723
W: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CO, CR, CU, CZ, DM, DZ, EC, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1313737	A1	20030528	EP 2001-956555	20010723
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004505084	T	20040219	JP 2002-515897	20010723
US 2003203896	A1	20031030	US 2003-343173	20030127
US 7259159	B2	20070821		

PRIORITY APPLN. INFO.: EP 2000-116385 A 20000728
WO 2001-EP8485 W 20010723

OTHER SOURCE(S): MARPAT 136:134796

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Acylguanidino derivs. I (n = 0-2; A and B = N, CH; X = CH2, NR1, O, S; Y = H, halogen, NR6R7, (un)substituted alkyl, (substituted)SO2, etc.; R1 = H, (C1-4)alkyl; R2 = OH, NH2, an amino acid bonded to CO through its amino group, SO2, NR6R7, CO2(un)substituted alkoxy, etc.; R3 = R4, R4C(O)R5, R4SO2R5, etc.; R5 = (C1-C4)alkylene or a direct bond; R6 and R7 = independently are H, (cyclo)alkyl, etc.) and their physiol. tolerable salts were prepared and tested as inhibitors. Thus Et 4-(6-chloropurin-9-yl)butyrate reacted with tert-Bu (2S)-3-amino-2-benzyloxycarbonylaminopropionate and the intermediate formed reacted further with 1,4,5,6-tetrahydropyrimidin-2-ylamine to yield II and its inhibitory concentration of the binding of kistrin to human vitronectin receptor (VnR) was 22.0 for K/VnR IC50 [nM]. Compds. I are vitronectin receptor antagonists and inhibitors of cell adhesion and bone resorption by osteoclasts and therefore are suitable for therapy and prophylaxis of illnesses based on the interaction between vitronectin receptors and their ligands in cell-cell or cell-matrix interaction processes or which can be prevented, alleviated or cured by influencing such interactions. I can be used for treating and preventing osteoporosis, or for inhibiting undesired angiogenesis or proliferation of cells of the vascular smooth muscles.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 17 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:453078 CAPLUS
DOCUMENT NUMBER: 135:46049
TITLE: Preparation of purine derivs. for the treatment of bone related disorders and cancer
INVENTOR(S): Weigele, Manfred; Shakespeare, William; Sawyer, Tomi K.; Sundaramoorthi, Rajeswari; Bohacek, Regine; Wang, Yihan; Metcalf, Chester A., III
PATENT ASSIGNEE(S): Ariad Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 168 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001044260	A2	20010621	WO 2000-US34417	20001218
WO 2001044260	A3	20020103		
WO 2001044260	A9	20020704		
WO 2001044260	A8	20030103		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2394646	A1	20010621	CA 2000-2394646	20001218

AU 200122772	A	20010625	AU 2001-22772		20001218
US 2002010159	A1	20020124	US 2000-740619		20001218
US 6420384	B2	20020716			
EP 1259520	A2	20021127	EP 2000-986551		20001218
EP 1259520	B1	20060524			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2004501062	T	20040115	JP 2001-544750		20001218
AT 327242	T	20060615	AT 2000-986551		20001218
PRIORITY APPLN. INFO.:			US 1999-172161P	P	19991217
			US 1999-172510P	P	19991217
			US 2000-240788P	P	20001016
			US 2000-740267	A	20001218
			US 2000-740619	A	20001218
			WO 2000-US34417	W	20001218

OTHER SOURCE(S): MARPAT 135:46049

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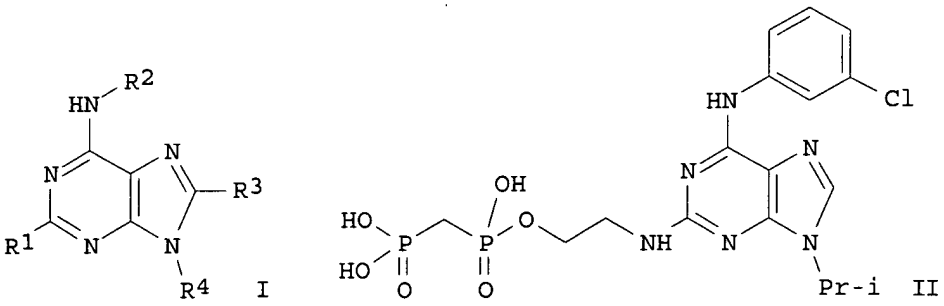

AB Purine derivs., such as I [R1, R3 = H, halogen, Y (Y = aliphatic, heteroaliph., aryl, heteroaryl, alkylaryl, alkylheteroaryl), ZR5 {Z = O, S, NR6; (R5, R6 = aliphatic, heteroaliph., aryl, heteroaryl, alkylaryl, alkylheteroaryl)}; R2 = Y; R4 = H, Y; whereby at least one of the R1, R2, R3 or R4 as defined above, is substituted by one or more phosphorus moieties] were prepared for the treatment of bone related disorders and cancer. Thus, purine derivative II was prepared via multistep synthetic sequence starting from 6-chloro-2-fluoro-9H-purine, 2-propanol, 3-chloroaniline, ethanolamine and methylenebis(phosphonic dichloride). The prepared purine derivs. were tested for their ability to inhibit protein kinases, to bind to bone, to inhibit bone resorption or to otherwise improve the relative dynamics of bone homeostasis.

L12 ANSWER 18 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER:	2001:453077 CAPLUS
DOCUMENT NUMBER:	135:46048
TITLE:	Preparation of purines with a phosphorus containing moiety for pharmaceutical use in the treatment of bone disorders
INVENTOR(S):	Weigele, Manfred; Sawyer, Tomi K.; Bohacek, Regine; Shakespeare, William C.; Sundaramoorthi, Rajeswari; Wang, Yihan; Dalgarno, David C.; Metcalf, Iii Chester A.
PATENT ASSIGNEE(S):	Ariad Pharmaceuticals, Inc., USA
SOURCE:	PCT Int. Appl., 128 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	5
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2001044259	A1	20010621	WO 2000-US34572		20001218
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU					
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR					
CA 2394573	A1	20010621	CA 2000-2394573		20001218
AU 200124417	A	20010625	AU 2001-24417		20001218
EP 1244679	A1	20021002	EP 2000-988184		20001218
EP 1244679	B1	20061115			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2003516998	T	20030520	JP 2001-544749		20001218
AT 327242	T	20060615	AT 2000-986551		20001218
AT 345349	T	20061215	AT 2000-988184		20001218
PRIORITY APPLN. INFO.:			US 1999-172510P	P	19991217
			US 2000-240788P	P	20001016
			US 1999-172161P	P	19991217
			US 2000-740267	A	20001218
			US 2000-740619	A	20001218
			WO 2000-US34572	W	20001218

OTHER SOURCE(S): MARPAT 135:46048
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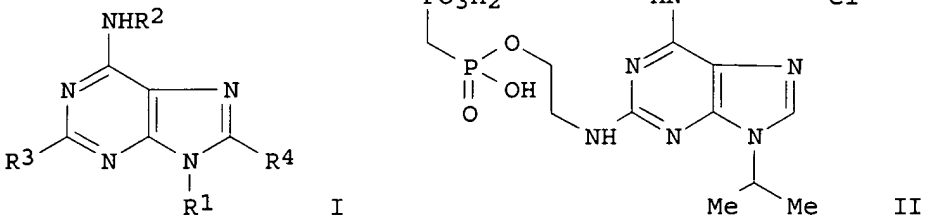

I II

AB Purines with a phosphorus containing moiety, such as I [R1 = H, alkyl, heteroalkyl, aryl, heteroaryl; R2 = phosphorus moiety containing alkyl, heteroalkyl, aryl, heteroaryl; R3 = H, halogen, phosphorus moiety containing alkyl, heteroalkyl, aryl, heteroaryl; R4 = H, halogen, alkyl, heteroalkyl, aryl, heteroaryl], were prepared for pharmaceutical use in the treatment of debilitating bone disorders, such as osteoporosis, Paget's disease, hyperparathyroidism, various cancers where bone tissue resorption is increased, and rheumatoid arthritis. Thus, purine II via a five step synthetic sequence starting from 2-amino-6-chloropurine 2-propanol, 3-chloroaniline, 2-aminoethanol, and methylenebis(phosphonic dichloride). The prepared phosphorus containing purines were tested for anti-resorption activity, Src kinase inhibition, and inhibition of tumor growth.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 19 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:453076 CAPLUS
DOCUMENT NUMBER: 135:46047

TITLE: Preparation of pyrimidine heterocycles with a phosphorus containing moiety for pharmaceutical use in the treatment of bone disorders

INVENTOR(S): Weigele, Manfred; Dalgarno, David C.; Luke, George P.; Sawyer, Tomi K.; Bohacek, Regine; Shakespeare, William C.; Sundaramoorthi, Rajeswari; Wang, Yihan; Metcalf, Chester A., III; Vu, Chi B.; Kawahata, Noriyuki H.

PATENT ASSIGNEE(S): Ariad Pharmaceuticals, Inc., USA

SOURCE: PCT Int. Appl., 186 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 5

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001044258	A1	20010621	WO 2000-US34487	20001218
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2394650	A1	20010621	CA 2000-2394650	20001218
AU 200124397	A	20010625	AU 2001-24397	20001218
US 2002132819	A1	20020919	US 2000-740653	20001218
EP 1246829	A1	20021009	EP 2000-988160	20001218
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003532632	T	20031105	JP 2001-544748	20001218
AT 327242	T	20060615	AT 2000-986551	20001218
US 2005096298	A1	20050505	US 2004-994962	20041122

PRIORITY APPLN. INFO.:

US 1999-172161P	P	19991217
US 1999-172510P	P	19991217
US 2000-240788P	P	20001016
US 2000-740653	A	20001218
US 2000-741619	A	20001218
US 2000-740267	A	20001218
US 2000-740619	A	20001218
WO 2000-US34487	W	20001218

OTHER SOURCE(S): MARPAT 135:46047

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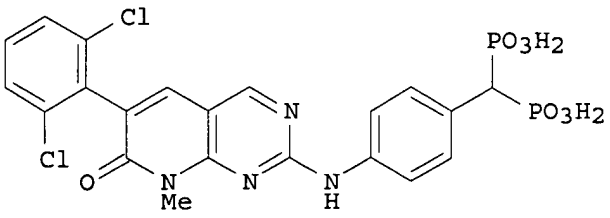


I

AB Heterocycles with a pyrimidine subunit and a phosphorus containing moiety, such as Hc-X-M-Y-M-Cy-M-Y-M-Z-Tb [Cy = aryl, heterocyclyl, heteroaryl, cycloalkyl; Hc = heterocycle containing a pyrimidine subunit; M = (CH2)n; Tb = phosphorus containing moiety; X, Y, Z = NR, O, S; R = H, alkyl, alkenyl, aryl, heterocyclyl, heteroaryl, etc.; n = 1 - 10], were prepared for

pharmaceutical use in the treatment of debilitating bone disorders, such as osteoporosis, Paget's disease, hyperparathyroidism, various cancers where bone tissue resorption is increased, and rheumatoid arthritis. Thus, pyrido[2,3-d]pyrimidine I was prepared in 41% yield by condensation of Br-4-C6H4CH[P(O)(OEt)2]2 with 2-amino-6-(2,6-dichlorophenyl)-8-methyl-pyrido[2,3-d]pyrimidin-7(8H)-one using Pd(OAc)2, Cs2CO3, and (S)-BINAP in toluene. The prepared phosphorus containing purines were tested for anti-resorption activity, Src kinase inhibition, and inhibition of tumor growth.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 1 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:907613 CAPLUS
DOCUMENT NUMBER: 147:269261
TITLE: Methods and compositions using adenosine A1 receptor antagonists for treating disorders associated with increased bone turnover and osteopenia
INVENTOR(S): Cronstein, Bruce N.; Kara, Firas Mohamed
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 53pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2007191279	A1	20070816	US 2007-705689	20070213
WO 2007095161	A2	20070823	WO 2007-US3656	20070213

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2006-773176P P 20060214
AB The invention provides methods and compns. for modulating osteoclastogenesis and for treating bone diseases characterized by bone loss or a decrease in bone mass or d., by administering a compound or agent that modulates the adenosine A1 receptor, in particular, an inhibitor or antagonist of the A1 receptor.

L12 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:524328 CAPLUS
DOCUMENT NUMBER: 147:363205
TITLE: Alterations in circulating osteoimmune factors may be responsible for high bone resorption rate in HIV-infected children and adolescents
AUTHOR(S): Mora, Stefano; Zamproni, Ilaria; Cafarelli, Laura; Giacomet, Vania; Erba, Paola; Zuccotti, Gianvincenzo; Vigano, Alessandra
CORPORATE SOURCE: Laboratory of Pediatric Endocrinology and BoNetwork, San Raffaele Scientific Institute, Milan, Italy
SOURCE: AIDS (Hagerstown, MD, United States) (2007), 21(9), 1129-1135
CODEN: AIDSET; ISSN: 0269-9370
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Bone metabolism derangements have been reported in HIV-infected children and adolescents. Nuclear factor kappa B ligand (RANKL) and osteoprotegerin potently stimulate and inhibit, resp., osteoclast formation and activity. We investigated the possible role of RANKL and osteoprotegerin on bone metabolism alterations in paediatric patients. A prospective controlled longitudinal study. Measurements were obtained before and 6 mo after switching antiretroviral regimen. We studied 27 vertically HIV-infected children and adolescents (aged 4.9-17.3 years) on long-term HAART (70.1

± 1.5 mo). All patients received lamivudine, stavudine and one protease inhibitor (PI). During follow-up, the PI was replaced with efavirenz and stavudine with tenofovir. We also enrolled 336 healthy children, aged 4.8-17.9 years. Concns. of bone-specific alkaline phosphatase (BALP), N-terminal telopeptide of type I collagen (NTx), RANKL, and osteoprotegerin were measured at baseline and 6 mo after switching. BALP serum concns. and NTx urine levels of HIV-infected patients were significantly higher than those of healthy children both at baseline and after 6 mo ($P < 0.001$). Baseline osteoprotegerin and RANKL concns. of HIV-infected patients were significantly higher than in healthy children ($P < 0.0001$). Both concns. decreased after 6 mo, and RANKL levels were no longer different to controls. At baseline the RANKL/osteoprotegerin ratio was significantly higher ($P = 0.02$) in HIV-infected children (0.27 ± 0.07) compared with healthy children (0.078 ± 0.01). A marked alteration in the RANKL/osteoprotegerin system is present in patients receiving PI-based HAART. Short-term data indicate that replacing stavudine and PI with tenofovir and efavirenz restores the RANKL/osteoprotegerin equilibrium, and may thus lead to a reduction in the bone resorption rate.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 3 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:140058 CAPLUS

DOCUMENT NUMBER: 144:362566

TITLE: Structural basis of Src tyrosine kinase inhibition with a new class of potent and selective trisubstituted purine-based compounds

AUTHOR(S): Dalgarno, David; Stehle, Thilo; Narula, Surinder; Schelling, Pierre; van Schravendijk, Marie Rose; Adams, Susan; Andrade, Lawrence; Keats, Jeff; Ram, Mary; Jin, Lei; Grossman, Trudy; MacNeil, Ian; Metcalf, Chester, III; Shakespeare, William; Wang, Yihan; Keenan, Terry; Sundaramoorthi, Raji; Bohacek, Regine; Weigele, Manfred; Sawyer, Tomi

CORPORATE SOURCE: ARIAD Pharmaceuticals, Cambridge, MA, 02139, USA

SOURCE: Chemical Biology & Drug Design (2006), 67(1), 46-57
CODEN: CBDDAL; ISSN: 1747-0277

PUBLISHER: Blackwell Publishing Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The tyrosine kinase pp60src (Src) is the prototypical member of a family of proteins that participate in a broad array of cellular signal transduction processes, including cell growth, differentiation, survival, adhesion, and migration. Abnormal Src family kinase (SFK) signaling has been linked to several disease states, including osteoporosis and cancer metastases. Src has thus emerged as a mol. target for the discovery of small-mol. inhibitors that regulate Src kinase activity by binding to the ATP pocket within the catalytic domain. Here, we present crystal structures of the kinase domain of Src in complex with two purine-based inhibitors: AP23451, a small-mol. inhibitor designed to inhibit Src-dependent bone resorption, and AP23464, a small-mol. inhibitor designed to inhibit the Src-dependent metastatic spread of cancer. In each case, a trisubstituted purine template core was elaborated using structure-based drug design to yield a potent Src kinase inhibitor. These structures represent early examples of high affinity purine-based Src family kinase-inhibitor complexes, and they provide a detailed view of the specific protein-ligand interactions that lead to potent inhibition of Src. In particular, the 3-hydroxyphenethyl N9 substituent of AP23464 forms unique interactions with the protein that are critical to the picomolar affinity of this compound for Src. The comparison of these new structures with two relevant kinase-inhibitor complexes provides a structural basis for the observed kinase inhibitory selectivity. Further comparisons reveal a concerted induced-fit movement between the N- and

C-terminal lobes of the kinase that correlates with the affinity of the ligand. Binding of the most potent inhibitor, AP23464, results in the largest induced-fit movement, which can be directly linked to interactions of the hydrophenethyl N9 substituent with a region at the interface between the two lobes. A less pronounced induced-fit movement is also observed in the Src-AP23451 complex. These new structures illustrate how the combination of structural, computational, and medicinal chemical can be used to rationalize the process of developing high affinity, selective tyrosine kinase inhibitors as potential therapeutic agents.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2006:100738 CAPLUS
DOCUMENT NUMBER: 144:198849
TITLE: Novel dosage form comprising modified-release and immediate-release active ingredients
INVENTOR(S): Vaya, Navin; Karan, Rajesh Singh; Sadanand, Sunil; Gupta, Vinod Kumar
PATENT ASSIGNEE(S): India
SOURCE: U.S. Pat. Appl. Publ., 49 pp., Cont.-in-part of U.S. Ser. No. 630,446.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2006024365	A1	20060202	US 2005-134633		20050519
IN 2002MU00697	A	20040529	IN 2002-MU697		20020805
IN 193042	A1	20040626			
IN 2002MU00699	A	20040529	IN 2002-MU699		20020805
IN 2003MU00080	A	20050204	IN 2003-MU80		20030122
IN 2003MU00082	A	20050204	IN 2003-MU82		20030122
US 2004096499	A1	20040520	US 2003-630446		20030729
PRIORITY APPLN. INFO.:			IN 2002-MU697	A	20020805
			IN 2002-MU699	A	20020805
			IN 2003-MU80	A	20030122
			IN 2003-MU82	A	20030122
			US 2003-630446	A2	20030729

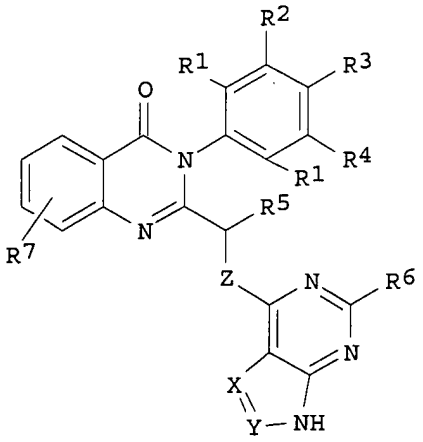
AB A dosage form comprising of a high dose, high solubility active ingredient as modified release and a low dose active ingredient as immediate release where the weight ratio of immediate release active ingredient and modified release active ingredient is from 1:10 to 1:15000 and the weight of modified release active ingredient per unit is from 500 mg to 1500 mg; a process for preparing the dosage form. Tablets containing 10 mg sodium pravastatin and 1000 mg niacin were prepared The release of sodium pravastatin after 24 h was 67.7%, and the release of niacin after 1 h was 84.1%.

L12 ANSWER 5 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:1259353 CAPLUS
DOCUMENT NUMBER: 144:22759
TITLE: Preparation of purine quinazolinones as inhibitors of human phosphatidylinositol 3-kinase delta
INVENTOR(S): Fowler, Kerry W.; Huang, Danwen; Kesicki, Edward A.; Ooi, Hua Chee; Oliver, Amy R.; Ruan, Fuqiang; Treiberg, Jennifer
PATENT ASSIGNEE(S): Icos Corporation, USA
SOURCE: PCT Int. Appl., 247 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2005113556	A1	20051201	WO 2005-US16778		20050512
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
AU 2005245875	A1	20051201	AU 2005-245875		20050512
CA 2566609	A1	20051201	CA 2005-2566609		20050512
WO 2005113554	A2	20051201	WO 2005-US16661		20050512
WO 2005113554	A3	20060406			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
EP 1761540	A1	20070314	EP 2005-752122		20050512
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, LV, MK, YU					
CN 101031569	A	20070905	CN 2005-80023449		20050512
JP 2007537291	T	20071220	JP 2007-513402		20050512
PRIORITY APPLN. INFO.:			US 2004-570784P	P	20040513
			WO 2005-US16778	W	20050512

OTHER SOURCE(S): CASREACT 144:22759; MARPAT 144:22759
GI



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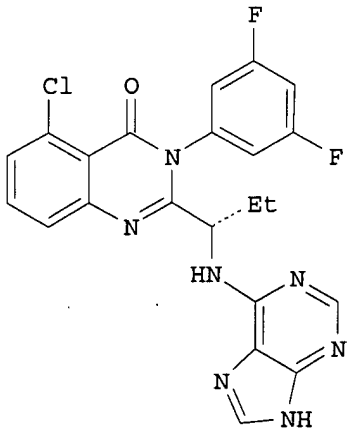


II

AB Quinazolinone derivs. of formula I [X, Y = N, (substituted) CH; Z = NH, O; R1-R3 = H, halo, alkyl; R4 = H, halo, OH, alkoxy, CN, acyl, etc.; R5 = alkyl, Ph, CH2C.tplbond.CH, etc.; R6 = H, halo, (substituted) NH2; R7 = alkyl, halo, CF3, etc.; ZR5 = alkylene] are prepared that inhibit PI3Kδ activity. Methods of inhibiting phosphatidylinositol 3-kinase delta isoform (PI3Kδ) activity, and methods of treating diseases, such as disorders of immunity and inflammation in which PI3Kδ plays a role in leukocyte function, using the compds. also are disclosed. Thus, II was prepared, and had EC50 value of 1.6 nM in human B lymphocyte assay.
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:1004719 CAPLUS
DOCUMENT NUMBER: 143:286448
TITLE: Preparation of fused bicyclic pyrimidine compounds as cathepsin K inhibitors
INVENTOR(S): Ohmoto, Kazuyuki; Hisaichi, Katsuya; Okuma, Motohiro; Tanaka, Makoto; Kawada, Naoki
PATENT ASSIGNEE(S): Ono Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 168 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005085210	A1	20050915	WO 2005-JP4580	20050309
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1724264	A1	20061122	EP 2005-720835	20050309
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
US 2007197510	A1	20070823	US 2006-592117	20060908
PRIORITY APPLN. INFO.:			JP 2004-68212 A	20040310
			WO 2005-JP4580 W	20050309

OTHER SOURCE(S): MARPAT 143:286448
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [ring A = carbocycle, heterocycle; ring B = heterocycle having at least one nitrogen; dotted line indicates single or double bond.; Y, Z = C, N; n = 0-10; R = H, substituent; further details on R are given.] were prepared For example, reaction of 5-(aminomethyl)-4-[(2,2-dimethylpropyl)amino]-2-pyrimidinecarbonitrile, e.g., prepared from 2,4-dichloro-5-(chloromethyl)pyrimidine in 4 steps, with N,N'-carbonyldiimidazole afforded compound II. In cathepsin K inhibition assays, the IC50 value of compound III was 2.9 nM. Compds. I are claimed

useful for the treatment of osteoporosis, arthritis, etc. Formulations are given.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

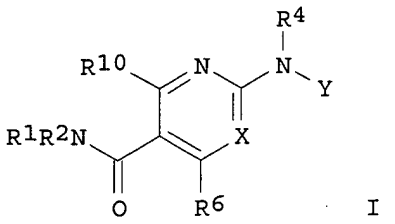
L12 ANSWER 7 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:823578 CAPLUS
DOCUMENT NUMBER: 143:229872
TITLE: Preparation of aminopyri(mi)dinecarboxamide CB2 modulators for use in combination with PDE4 inhibitors for treating pain, immune, inflammatory and rheumatic diseases
INVENTOR(S): Green, Richard Howard; Brown, Andrew James; Connor, Helen Elizabeth; Eatherton, Andrew John; Giblin, Gerard Martin Paul; Jandu, Karamjit Singh; Knowles, Richard Graham; Mitchell, William Leonard; Naylor, Alan; O'Shaughnessy, Celestine Theresa; Palombi, Giovanni; Rawlings, Derek Anthony; Slingsby, Brian Peter; Tralau-Stewart, Catherine Jane; Whittington, Andrew Richard; Williamson, Richard Alexander
PATENT ASSIGNEE(S): Glaxo Group Limited, UK; Doughty, Jennifer Margaret
SOURCE: PCT Int. Appl., 192 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005074939	A1	20050818	WO 2005-GB348	20050201
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1732561	A1	20061220	EP 2005-702088	20050201
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, HR, LV				
JP 2007520538	T	20070726	JP 2006-551906	20050201

PRIORITY APPLN. INFO.: GB 2004-2355 A 20040203
WO 2005-GB348 W 20050201

OTHER SOURCE(S): MARPAT 143:229872
GI



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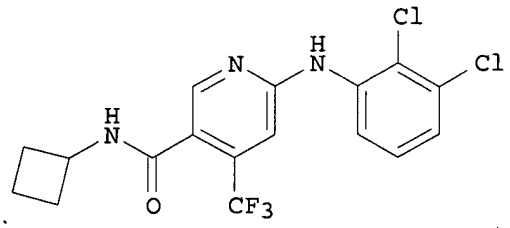


II

AB The invention is related to combination of one or more CB2 modulators of formula I [X = CH, N; Y = (un)substituted Ph; R1 = H, cyclo/alkyl, (un)substituted haloalkyl; R2 = C(R7)2R3; R3 = (un)substituted non-aromatic heterocyclyl, cycloalk(en)yl, 5-6 membered aromatic heterocyclyl, etc.; R4 = H, COMe, SO2Me, cyclo/alkyl, (un)substituted haloalkyl; R6 = Me, Cl, CHmFn; n = 1-3; m = 0-2; (n + m) = 3; R7 = H, alkyl; when X = CH, R6 = Cl, or (un)substituted alkyl and R10 = H, or R10 = Cl, or (un)substituted alkyl and R10 = H; and their pharmaceutically acceptable salts] and one or more PDE4 inhibitors useful for treating conditions which are mediated by the activity of CB2 receptors or conditions which are mediated by PDE4, such as an immune disorder, an inflammatory disorder, pain, rheumatoid. The invention is also related to the preparation of CB2 modulators I. For example, reacting cyclobutylamine with 6-(2,3-dichlorophenylamino)-4-trifluoromethylnicotinic acid (preparation given) gave II in 81% yield. Selected I had EC50 values of >300 nM but <1000 nM and efficacy value of >50% at the cloned human cannabinoid CB2 receptor. Three formulations are given.

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

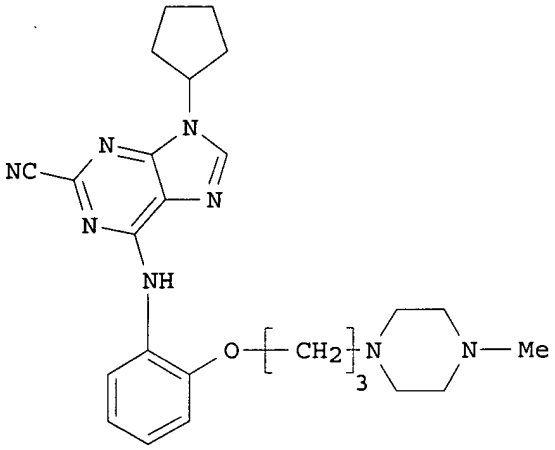
L12 ANSWER 8 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:349616 CAPLUS
DOCUMENT NUMBER: 143:125435
TITLE: Nephrotoxicity of several newer agents
AUTHOR(S): Henrich, William L.
CORPORATE SOURCE: Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA
SOURCE: Kidney International, Supplement (2005), 94, S107-S109
CODEN: KISUDF; ISSN: 0098-6577
PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The article discusses several drugs implicated as nephrotoxins in the recent literature, including cyclooxygenase-2 inhibitors, bisphosphonates, i.v. IgG, cidofivir, and adefovir.

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 9 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:886368 CAPLUS
DOCUMENT NUMBER: 141:360213
TITLE: Novel Purine Nitrile Derived Inhibitors of the Cysteine Protease Cathepsin K

AUTHOR(S): Altmann, Eva; Cowan-Jacob, Sandra W.; Missbach, Martin
CORPORATE SOURCE: Novartis Institutes for BioMedical Research, Basel, CH-4002, Switz.
SOURCE: Journal of Medicinal Chemistry (2004), 47(24), 5833-5836
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:360213
GI



I

AB Starting from a high-throughput screening hit, novel cathepsin K inhibitors have been developed based on a purine scaffold. High-resolution X-ray structures of several derivs. have revealed the binding mode of these unique cysteine protease inhibitors.
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2006:436804 CAPLUS
DOCUMENT NUMBER: 144:456516
TITLE: Use of A3AR agonists for the treatment of accelerated bone resorption
INVENTOR(S): Fishman, Pnina; Bar Yehuda, Sara; Madi, Lea
PATENT ASSIGNEE(S): Can-Fite Biopharma Ltd., Israel
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2006048884	A1	20060511	WO 2005-IL1166		20051108
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
AU 2005302090	A1	20060511	AU 2005-302090		20051108
CA 2586845	A1	20060511	CA 2005-2586845		20051108
EP 1811982	A1	20070801	EP 2005-799989		20051108
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR					
CN 101072554	A	20071114	CN 2005-80038001		20051108
KR 2007085839	A	20070827	KR 2007-712806		20070607
PRIORITY APPLN. INFO.:			US 2004-625564P	P	20041108
			WO 2005-IL1166	W	20051108

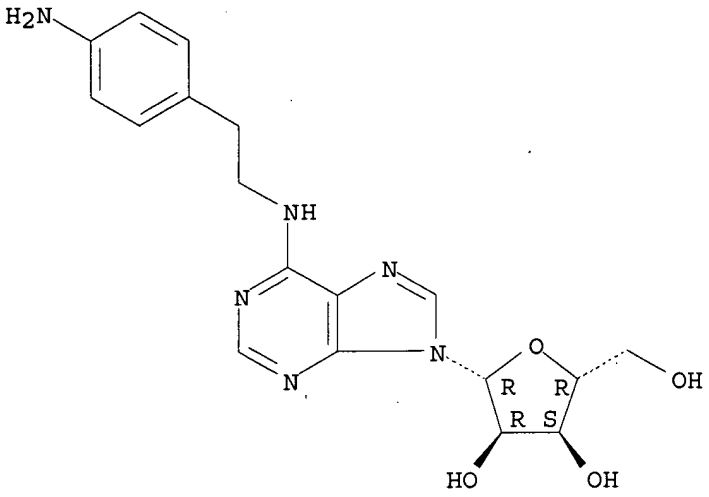
OTHER SOURCE(S): MARPAT 144:456516

AB The present invention concerns the use of an A3 adenosine receptor agonist (A3AR agonist) for treatment of accelerated bone resorption, particularly, inflammation induced bone resorption. Specifically, there is provided by the present invention a method and pharmaceutical composition for treatment of said condition, the A3AR agonist being formulated as a pharmaceutical composition which is administered to a subject having accelerated bone resorption. The invention also provides the use of A3AR agonist in the preparation of said pharmaceutical composition For example, oral dosages containing N6-(3-iodobenzyl)-adenosine-5'-N-methyluronamide was able to treat the inflammatory arthritis in animal model.

IT 89705-21-5, N6-[-2-(4-Aminophenyl)ethyl]adenosine
152918-18-8, N6-(3-Iodobenzyl)-adenosine-5'-N-methyluronamide
152918-27-9 163042-96-4, 2-Chloro-N6-(3-Iodobenzyl)-adenosine-5'-N-methyluronamide
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. containing A3AR agonists for the treatment of accelerated bone resorption and inflammatory arthritis)

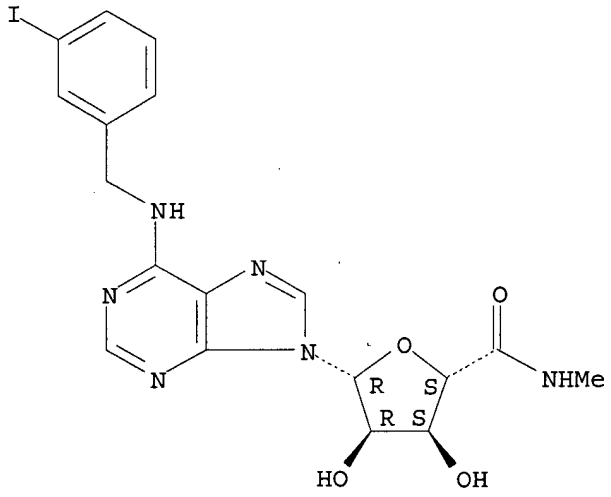
RN 89705-21-5 CAPLUS
CN Adenosine, N-[2-(4-aminophenyl)ethyl]- (CA INDEX NAME)

Absolute stereochemistry.



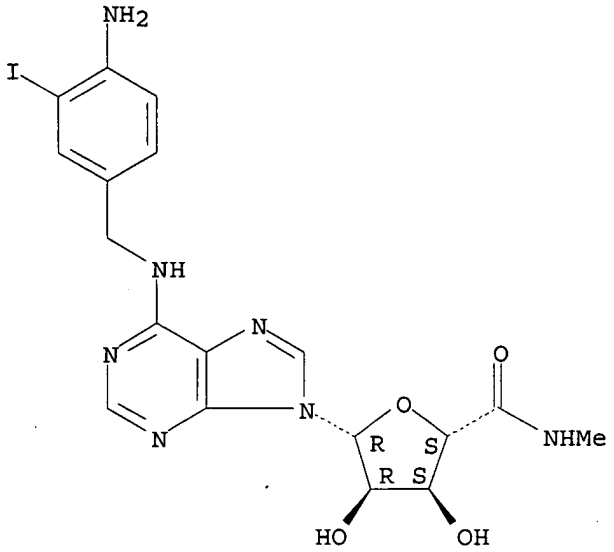
RN 152918-18-8 CAPLUS
CN β-D-Ribofuranuronamide, 1-deoxy-1-[6-[[(3-iodophenyl)methyl]amino]-9H-purin-9-yl]-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.



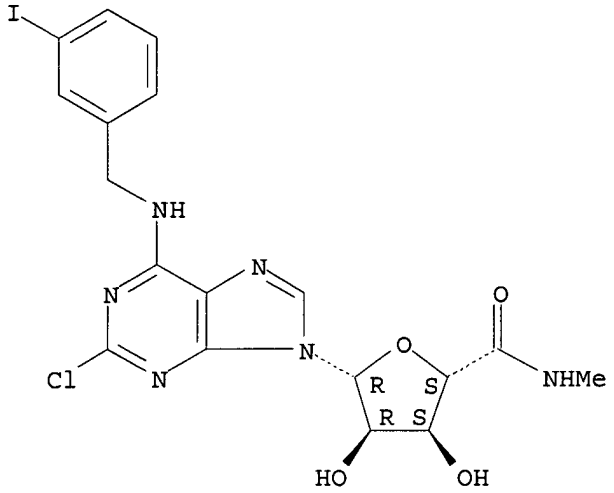
RN 152918-27-9 CAPLUS
CN β-D-Ribofuranuronamide, 1-[6-[[(4-amino-3-iodophenyl)methyl]amino]-9H-purin-9-yl]-1-deoxy-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.



RN 163042-96-4 CAPLUS
CN β-D-Ribofuranuronamide, 1-[2-chloro-6-[[(3-iodophenyl)methyl]amino]-9H-purin-9-yl]-1-deoxy-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1987:612277 CAPLUS
DOCUMENT NUMBER: 107:212277
TITLE: Characterization of adenosine receptors in bone. Studies on the effect of adenosine analogs on cyclic AMP formation and bone resorption in cultured mouse calvaria
AUTHOR(S): Lerner, Ulf H.; Sahlberg, K.; Fredholm, B. B.
CORPORATE SOURCE: Dep. Oral Pathol., Univ. Umea, Umea, S-901 87, Swed.
SOURCE: Acta Physiologica Scandinavica (1987), 131(2), 287-96
CODEN: APSCAX; ISSN: 0001-6772
DOCUMENT TYPE: Journal
LANGUAGE: English

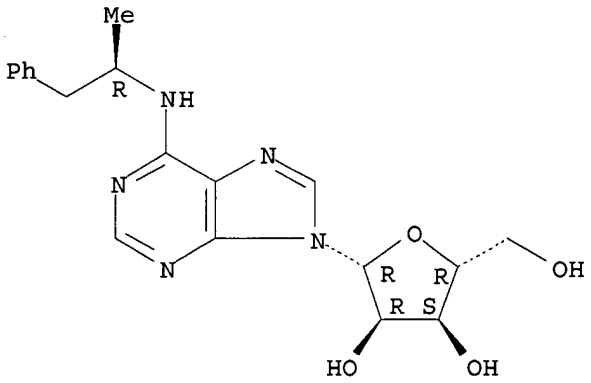
AB The effect of different adenosine analogs on cAMP formation and bone resorption was studied in cultured mouse calvarial bones. 5'-N-Ethylcarboxamidoadenosine (NECA), R-N6-phenylisopropyladenosine (PIA), N6-cyclohexyladenosine (CHA), and 2-chloroadenosine all stimulated cAMP formation with a threshold close to 1μM; NECA was the most potent agonist. Theophylline (10 and 100 μM) inhibited the cAMP accumulation induced by NECA and 2-chloroadenosine (30 and 300 μM), dose dependently. There was no inhibition of cAMP formation by PIA and CHA in forskolin-treated bone tissue. SQ 22, 536 and 2',5'-dideoxyadenosine (100 μM) both inhibited rolipram-stimulated cAMP formation. The cAMP accumulation in osteoblast-like cells from neonatal mouse calvarial bones was stimulated by NECA (10 and 100 μM) and 2-chloroadenosine (100 μM). 2-Chloroadenosine (10 and 30 μM), but not NECA, PIA, nor CHA, caused a dose-dependent stimulation of 45Ca release in both 48- and 120-h culture. The effect of 2-chloroadenosine on 45Ca release could not be antagonized by theophylline. Neither NECA, PIA, CHA, nor 2-chloroadenosine could affect parathormone (PTH)-stimulated 45Ca release in short term cultures (6, 24 h). By contrast, stimulation of cAMP formation by forskolin or dibutyryl cAMP caused a rapid (6 h) inhibition of PTH-stimulated bone resorption. The results demonstrate functional A2 and P-site receptors in mouse calvaria and osteoblast-like cells, but no A1-receptor was detected. These adenosine receptors regulate cAMP, but are not intimately linked to bone resorption. The Ca mobilization induced by 2-chloroadenosine appears to be unrelated to adenosine receptors.

IT 38594-96-6, R-N6-Phenylisopropyladenosine
RL: BIOL (Biological study)
(bone resorption and cAMP formation response to, receptors mediation of)

RN 38594-96-6 CAPLUS

CN Adenosine, N-[(1R)-1-methyl-2-phenylethyl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L4 ANSWER 3 OF 3 MEDLINE on STN

ACCESSION NUMBER: 2006532317 MEDLINE

DOCUMENT NUMBER: PubMed ID: 16956430

TITLE: IB-MECA, an A3 adenosine receptor agonist prevents bone resorption in rats with adjuvant induced arthritis.

AUTHOR: Rath-Wolfson L; Bar-Yehuda S; Madi L; Ochaion A; Cohen S; Zabutti A; Fishman P

CORPORATE SOURCE: Can-Fite BioPharma Ltd., Kiryat-Matalon, Petah-Tikva, Israel.

SOURCE: Clinical and experimental rheumatology, (2006 Jul-Aug) Vol. 24, No. 4, pp. 400-6.
Journal code: 8308521. ISSN: 0392-856X.

PUB. COUNTRY: Italy
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200612
ENTRY DATE: Entered STN: 8 Sep 2006
Last Updated on STN: 19 Dec 2006
Entered Medline: 12 Dec 2006

AB OBJECTIVES: The anti-inflammatory effect of adenosine is partially mediated via the A3 adenosine receptor (A3AR), a Gi protein associated cell surface receptor. The highly selective A3AR agonist, IB-MECA was earlier shown to prevent the clinical and pathological manifestations of arthritis in experimental animal models of collagen and adjuvant induced arthritis (AIA). In this study we tested the effect of IB-MECA on the prevention of bone resorption in AIA rats and looked at the molecular mechanism of action. METHODS: Rats with AIA were treated orally twice daily with IB-MECA starting upon onset of disease and the clinical score was evaluated every other day. At study termination the foot, knee and hip region of both vehicle and IB-MECA treated animals were subjected to histomorphometric analysis. Western blot analysis was carried out on paw protein extracts. RESULTS: IB-MECA ameliorated the clinical manifestations of the disease and reduced pannus and fibrosis formation, attenuated cartilage and bone destruction and decreased the number of osteoclasts. In cell protein extracts derived from paw of AIA rats, A3AR was highly expressed in comparison to naive animals. In paw extracts derived from IB-MECA treated AIA rats, down-regulation of the A3AR protein expression level was noted. PI3K, PKB/Akt, IKK, NF-kappaB, TNF-alpha and RANKL were down-regulated whereas caspase 3 was up-regulated. CONCLUSION: IB-MECA, a small highly bioavailable molecule, induces modulation of proteins which control survival and apoptosis resulting in the amelioration of the inflammatory process and the preservation of bone mass in AIA rats.

L6 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2007:619807 CAPLUS
DOCUMENT NUMBER: 147:2017
TITLE: Use of A3 adenosine receptor agonist in osteoarthritis treatment
INVENTOR(S): Fishman, Pnina
PATENT ASSIGNEE(S): Can-Fite Biopharma Ltd., Israel
SOURCE: PCT Int. Appl., 32pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007063538	A1	20070607	WO 2006-IL1374	20061129

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

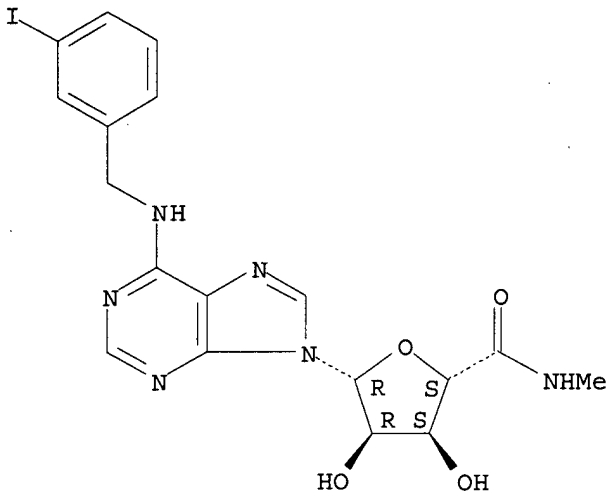
PRIORITY APPLN. INFO.: US 2005-740631P P 20051130

AB The present invention provides the use of an A3 adenosine receptor agonist (A3AR agonist) for the preparation of a pharmaceutical composition for the treatment of a mammal subject having osteoarthritis (OA), the amount of the A3AR agonist being effective to treat or prevent the development of OA. Preferred A3AR agonists in accordance with the invention are IB-MECA and CI-IB-MECA. The A3AR agonist may be administered in combination with another drug, such as, Methotrexate (MTX); The invention also provides pharmaceutical compns. for treatment of osteoarthritis comprising an amount of an A3AR agonist.

IT 152918-18-8, IB-MECA 163042-96-4, Ci-IB-MECA
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of A3 adenosine receptor agonist in osteoarthritis treatment)

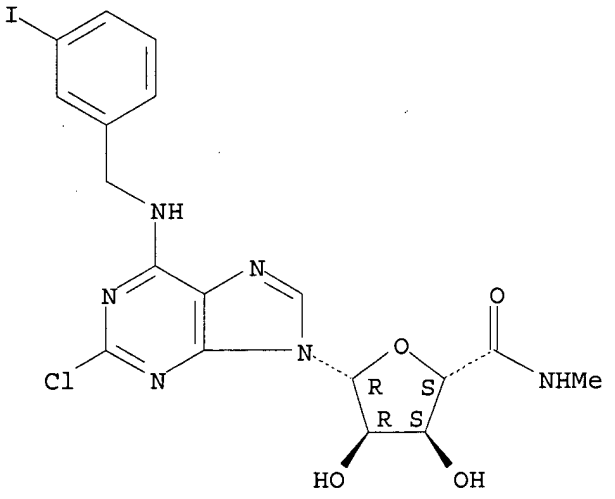
RN 152918-18-8 CAPLUS
CN β-D-Ribofuranuronamide, 1-deoxy-1-[6-[[(3-iodophenyl)methyl]amino]-9H-purin-9-yl]-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.



RN 163042-96-4 CAPLUS
CN β-D-Ribofuranuronamide, 1-[2-chloro-6-[[(3-iodophenyl)methyl]amino]-9H-purin-9-yl]-1-deoxy-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:1004549 CAPLUS
DOCUMENT NUMBER: 143:286636
TITLE: Preparation of nucleosides as adenosine receptors and used for the treatment of pain and inflammation
INVENTOR(S): Pritchard, Martyn; Ouzman, Jacqueline; Savory, Edward; Brown, Giles
PATENT ASSIGNEE(S): Cambridge Biotechnology Limited, UK
SOURCE: PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005084653	A2	20050915	WO 2005-GB800	20050304
WO 2005084653	A3	20060518		
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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2004079329	A2	20040916	WO 2004-GB902	20040305
WO 2004079329	A3	20041209		
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CA 2557285	A1	20050915	CA 2005-2557285	20050304
EP 1749016	A2	20070207	EP 2005-717878	20050304
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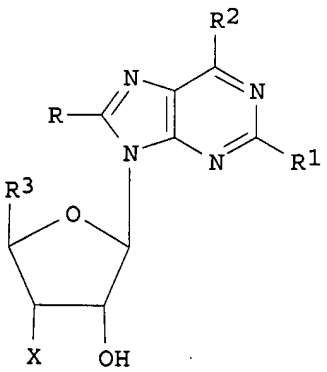
CN 1946732	A	20070411	CN 2005-80007119	20050304
BR 2005008488	A	20070731	BR 2005-8488	20050304
JP 2007526291	T	20070913	JP 2007-501345	20050304
NO 2006004365	A	20061122	NO 2006-4365	20060926
KR 2007004792	A	20070109	KR 2006-720304	20060929
IN 2006CN03674	A	20070706	IN 2006-CN3674	20061005
PRIORITY APPLN. INFO.:			GB 2004-5009 A	20040305
			GB 2004-5012 A	20040305
			WO 2004-GB902 A	20040305
			GB 2004-12261 A	20040602
			GB 2004-12262 A	20040602
			GB 2004-13627 A	20040618
			GB 2004-19718 A	20040906
			GB 2004-20063 A	20040909
			GB 2004-20615 A	20040916
			GB 2003-5153 A	20030307
			WO 2005-GB800 W	20050304
OTHER SOURCE(S):	MARPAT 143:286636			

GI



I

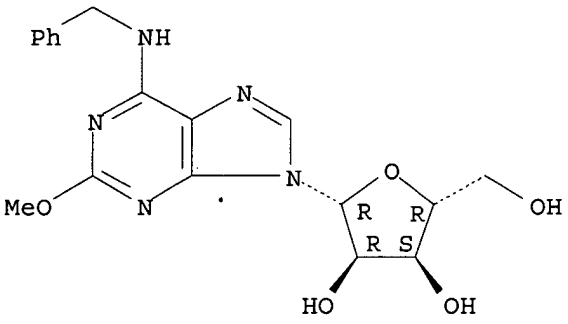
AB Nucleosides I, wherein X is H, OH; R is H, Me; R1 is H, alkoxy, OCH2-cyclopropyl, OCH2-cyclopentyl, phenoxy, OCH2CH2OH, OCH2CH2F2, (5-indanyl)oxy, alkylamino, cyclo-alkylamino, exo-norbornane, amino, phenylamino; R2 is NH2, CH2OH, NMe2, methylamino, isoamyl; R3 is CH2OH, amide, CH2NHCOPr-n, CH2NHCONHEt; were prepared and used for the treatment of pain and inflammation. Title nucleosides were prepared and used the treatment of pain associated with cancer, pancreatic pain, pain associated with HIV infection, chronic neuropathic pain, lower back pain, failed back surgery pain, back pain, post-operative pain, post phys. trauma pain, cardiac pain, chest pain, joint pain, neck pain, bowel pain, phantom limb pain, obstetric pain, acute herpes zoster pain, acute pancreatitis breakthrough pain, or for the prevention, treatment, or amelioration of neuropathic or other pain caused by, or associated with diabetic neuropathy, poly-neuropathy, fibromyalgia, myo-fascial pain syndrome, osteoarthritis, post herpetic neuralgia, rheumatoid arthritis, sciatica/lumbar radiculopathy, spinal stenosis, trigeminal neuralgia, renal colic, dysmenorhoea/endometriosis. Thus, I (R = H, R1 = OMe, R2 = NH1, R3 = CH2OH) was prepared and tested for the treatment of pain and inflammation.

IT 864062-03-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of nucleosides as adenosine receptors and used for the treatment of pain and inflammation)

RN 864062-03-3 CAPLUS

CN Adenosine, 2-methoxy-N-(phenylmethyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:756969 CAPLUS
DOCUMENT NUMBER: 141:254620
TITLE: Identification of therapeutic compounds
INVENTOR(S): Richardson, Peter
PATENT ASSIGNEE(S): Cambridge Biotechnology Ltd., UK
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004079329	A2	20040916	WO 2004-GB902	20040305
WO 2004079329	A3	20041209		

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GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE,
BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU,
MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2004217731	A1	20040916	AU 2004-217731		20040305
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US 2007059773	A1	20070315	US 2004-547462		20040305
AU 2005218997	A1	20050915	AU 2005-218997		20050304
CA 2557285	A1	20050915	CA 2005-2557285		20050304
WO 2005084653	A2	20050915	WO 2005-GB800		20050304
WO 2005084653	A3	20060518			

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RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
MR, NE, SN, TD, TG

EP 1749016	A2	20070207	EP 2005-717878		20050304
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NO 2006004365	A	20061122	NO 2006-4365		20060926
KR 2007004792	A	20070109	KR 2006-720304		20060929
PRIORITY APPLN. INFO.:			GB 2003-5153	A	20030307
			GB 2004-5009	A	20040305
			GB 2004-5012	A	20040305
			WO 2004-GB902	W	20040305
			GB 2004-12261	A	20040602
			GB 2004-12262	A	20040602
			GB 2004-13627	A	20040618
			GB 2004-19718	A	20040906
			GB 2004-20063	A	20040909
			GB 2004-20615	A	20040916
			WO 2005-GB800	W	20050304

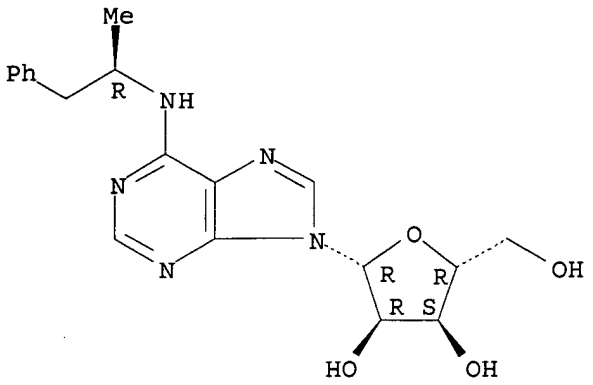
AB Methods for identifying potential therapeutic agents involve determining the affinity and/or efficacy of a test compound for an adenosine receptor at a relatively high pH and at a relatively low pH. Compds. with greater affinity and/or efficacy at the low pH are identified as potential therapeutic agents, in particular for the treatment of pain or inflammation.

IT 38594-96-6 38594-97-7
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(identification of therapeutic compds.)

RN 38594-96-6 CAPLUS

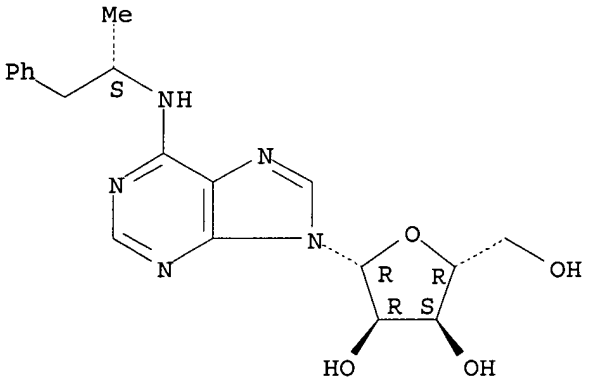
CN Adenosine, N-[(1R)-1-methyl-2-phenylethyl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 38594-97-7 CAPLUS
CN Adenosine, N-[(1S)-1-methyl-2-phenylethyl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



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L2             2 S ADENOSINE/TI (P) BONE LOSS/TI
L3            16 S ADENOSINE/TI (P) BONE RESORPTION/TI
L4             1 S PURINE DERIVATIVES/TI (P) BONE RESORPTION/TI
L5             1 S PURINE DERIVATIV?/TI (P) BONE RESORPTION/TI
L6             2 S PURINES/TI (P) BONE RESORPTION/TI
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L12            0 S ADENINE?/TI (P) BONE LOSS/TI
L13            0 S ADENINNSINE?/TI (P) BONE LOSS/TI
L14            2 S ADENOSINE?/TI (P) BONE LOSS/TI
L15            2 S PURINE?(P) BONE RESORPTION (P) PREVENT?
L16           10 S PURINE?(P) BONE RESORPTION (P) TREAT?
L17           24 S PURINE?(P) BONE RESORPTION
L18           14 S L17 NOT L16
L19           22 S ADENINE? (P) BONE RESORPTION
L20           22 S L19 NOT L3
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=> d his

     (FILE 'HOME' ENTERED AT 11:27:14 ON 21 JAN 2008)

     FILE 'REGISTRY' ENTERED AT 11:27:38 ON 21 JAN 2008
L1             STRUCTURE UPLOADED
L2            50 S L1 SSS SAM
L3         91204 S L1 SSS FULL
L4             STRUCTURE UPLOADED
L5            50 S L4 SSS SAM
L6         15650 S L4 SSS FULL

     FILE 'CAPLUS, MEDLINE' ENTERED AT 11:31:20 ON 21 JAN 2008
L7        280832 S L3
L8           383 S L3 AND BONE RESORPTION
L9            26 S L8 AND PREVENT?
L10          146 S L8 AND TREAT?
L11         9516 S L6
L12           19 S L11 AND BONE RESORPTION
```

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=> d his

     (FILE 'HOME' ENTERED AT 12:10:50 ON 21 JAN 2008)

     FILE 'REGISTRY' ENTERED AT 12:11:00 ON 21 JAN 2008
L1             STRUCTURE UPLOADED
L2          50 S L1 SSS SAM
L3       14257 S L1 SSS FUL

     FILE 'CAPLUS, MEDLINE' ENTERED AT 12:11:42 ON 21 JAN 2008
L4           3 S L3 AND BONE RESORPTION
L5           0 S L3 AND BONE LOSS
L6           3 S L3 AND OSTEOARTHRITIS
L7           0 S L3 AND BONE REDUCTION
L8           0 S L3 AND LOSS OF BONE
L9           0 S L3 AND BONE DECREASE?
```

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=> d his

     (FILE 'HOME' ENTERED AT 12:39:23 ON 21 JAN 2008)

     FILE 'REGISTRY' ENTERED AT 12:39:38 ON 21 JAN 2008
L1             STRUCTURE UPLOADED
L2              15 S L1 SSS SAM
L3             315 S L1 SSS FULL

     FILE 'CAPLUS, MEDLINE' ENTERED AT 12:40:39 ON 21 JAN 2008
L4               0 S L3 AND BONE RESORPTION?
L5               0 S L3 AND BONE LOSS
L6               STRUCTURE UPLOADED

     FILE 'REGISTRY' ENTERED AT 12:44:45 ON 21 JAN 2008
L7               STRUCTURE UPLOADED
L8              50 S L7
L9            2072 S L7 SSS FULL

     FILE 'CAPLUS, MEDLINE' ENTERED AT 12:46:07 ON 21 JAN 2008
L10          10358 S L9
L11              0 S L10 AND BONE RESPRPTION
L12              7 S L10 AND BONE RESORPTION
L13              0 S L10 AND BONE LOSS
L14             10 S L10 AND OSTEOARTHRITIS?

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